Antioxidants for pain in chronic pancreatitis

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[Intervention Review]

Antioxidants for pain in chronic pancreatitis

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ABSTRACT

Background

Reduced intake and absorption of antioxidants due to pain and malabsorption are probable causes of the lower levels of antioxidants observed in patients with chronic pancreatitis (CP). Improving the status of antioxidants might be effective in slowing the disease process and reducing pain in CP.

Objectives

To assess the benefits and harms of antioxidants for the treatment of pain in patients with CP.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and the Conference Proceedings Citation Index from inception to October 2012. Two review authors performed the selection of trials independently.

Selection criteria

We included all randomised controlled trials (RCTs) evaluating antioxidants for treatment of pain in CP. All trials were included irrespective of blinding, numbers of participants randomly assigned and language of the article.

Data collection and analysis

Two review authors extracted data independently. The risk of bias of included trials was assessed. Study authors were asked for additional information in the case of missing data.

Main results

Twelve RCTs with a total of 585 participants were included. Six trials were double-blinded, placebo-controlled studies, and the other six trials were of less adequate methodology. Most trials were small and had high rates of dropout. Eleven of the 12 included trials described the effects of antioxidants on chronic abdominal pain in chronic pancreatitis. Pain as measured on a visual analogue scale (VAS, scale range 0 to 10) after one to six months was less in the antioxidant group than in the control group (mean difference (MD) -0.33, 95% confidence interval (CI) -0.64 to -0.02, P value 0.04, moderate-quality evidence). The number of pain-free participants was not statistically significantly different (risk ratio (RR) 1.73, 95% CI 0.95 to 3.15, P value 0.07, low-quality evidence). More

adverse events were observed in the antioxidant group, both in the parallel trials (RR 4.43, 95% CI 1.60 to 12.29, P value 0.0004, moderate-quality evidence) and in the cross-over trials (RR 5.80, 95% CI 1.56 to 21.53, P value 0.0009, moderate-quality evidence). Adverse events occurred in 16% of participants and were mostly mild (e.g. headache, gastrointestinal complaints), but were sufficient to make participants stop antioxidant use. Other important outcomes such as use of analgesics, exacerbation of pancreatitis and quality of life were rarely reported. One trial from 1991 evaluated the effects of antioxidants on acute pain during exacerbation of chronic pancreatitis and found that a significantly higher proportion of participants in the antioxidant group experienced pain relief. This trial was conducted more than 25 years ago and has not been reproduced since that time. Therefore, additional trials are needed before reliable conclusions can be drawn.

Authors' conclusions

Current evidence shows that antioxidants can reduce pain slightly in patients with chronic pancreatitis. The clinical relevance of this small reduction is uncertain, and more evidence is needed. Adverse events in one of six patients may prevent the use of antioxidants. Effects of antioxidants on other outcome measures, such as use of analgesics, exacerbation of pancreatitis and quality of life remain uncertain because reliable data are not available.

PLAIN LANGUAGE SUMMARY

Antioxidants to reduce pain in chronic pancreatitis

Chronic pancreatitis is a persistent inflammation of the pancreas that in the long run can cause irreparable damage. The major causes of chronic pancreatitis are genetics, alcohol toxicity and other conditions that might damage or obstruct the pancreas. This inflammation can cause pain that often is severe and leaves patients socially isolated and unable to perform their jobs. Unfortunately, treatment options are scarce, and often strong morphine-like pain medications are needed. Patients might benefit from alternative medication without the adverse effects associated with morphine-like medication. This review summarises the evidence from randomised trials on the effects of antioxidants in chronic pancreatitis. Antioxidants are substances that prevent damage to cells caused by toxic byproducts of oxygen in the body. Levels of these byproducts are increased in chronic pancreatitis. Antioxidants constitute a large group that contains many natural and man-made products. Examples include vitamin C, vitamin E, flavonoids (present in tea and cocoa) and many specialised medications. We found 12 randomised trials on this topic. The quality of these trials was mixed, and many had small sample sizes and high rates of dropout. Evidence shows that antioxidants may reduce pain in patients with chronic pancreatitis, but the reported reduction in pain was small. Whether this small decrease really had an impact on patients' complaints is not clear. Given the methodological problems of these trials, a strong conclusion could not be drawn. Use of antioxidants resulted in adverse effects in about 16% of study participants. Most adverse effects were mild, such as headache, nausea and constipation. However, participants who developed these adverse effects tended to stop using antioxidant medication. Other outcomes important for decision making such as use of analgesics, rate of exacerbation of pancreatitis and quality of life, were not very well reported. Therefore, we were unable to reach conclusions on these outcomes.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antioxidant versus control intervention for pain in chronic pancreatitis

Patient or population: patients with pain in chronic pancreatitis
Intervention: antioxidant versus control intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Antioxidant versus control intervention				
Pain visual analogue score Scale from 0 to 10		Mean pain visual analogue score in the intervention groups was **0.33 lower** (0.64 to 0.02 lower)		129 (4 studies)	⊕⊕⊕○ **moderate**[a]	Clinical relevance is limited because of small absolute decrease (0.33 points on a scale of 10 points)
Pain-free participants	**297 per 1000**	**514 per 1000** (282 to 935)	**RR 1.73** (0.95 to 3.15)	264 (3 studies)	⊕⊕○○ **low**[b,c]	
Adverse effects-parallel trials	**40 per 1000**	**177 per 1000** (64 to 492)	**RR 4.43** (1.60 to 12.29)	212 (3 studies)	⊕⊕⊕○ **moderate**[d]	Overall, adverse effects occurred in 16% of antioxidant group. Most adverse effects were mild in nature (headache, gastrointestinal symptoms)
Adverse effects-crossover trials (unpaired data)	**10 per 1000**	**60 per 1000** (16 to 224)	**RR 5.80** (1.56 to 21.53)	192 (5 studies)	⊕⊕⊕○ **moderate**[d]	Overall, adverse effects occurred in 16% of antioxidant group. Most adverse effects were mild in nature

				(headache, gastrointestinal symptoms)

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI.
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] 3 trials had high dropout rates. 1 trial also suffered from selective reporting of outcomes.
[b] All trials had high rates of dropout. 1 trial was not blinded, and another suffered from selective reporting.
[c] Heterogeneity was high between trials (I^2 = 71%).
[d] Most trials had high rates of dropout. Some had additional methodological limitations (see Figure 2).

BACKGROUND

Description of the condition

Chronic pancreatitis (CP) is an irreversible inflammatory process of the pancreas, characterised by damage to the pancreas parenchyme and loss of pancreatic function. The annual incidence and prevalence are estimated at around seven and 20 per 100,000, respectively (Dite 2001; Levy 2006; Spanier 2008). Development of CP is probably due to a complex interrelationship of etiological factors, of which the most important are alcohol toxicity, genetic predisposition, duct obstruction, trauma, pancreas divisum and autoimmune pancreatitis (Spanier 2008; Witt 2007).

Abdominal pain is the most prominent symptom in CP (van Esch 2006; Witt 2007). Pain in CP can be severe, debilitating and challenging to treat. Several options for treatment of pain are known, including lifestyle recommendations, use of analgesics and endoscopic or surgical intervention (Apte 1999; Gachago 2008). For many patients, however, these options may be inappropriate or may prove ineffective. Furthermore, long-standing disease results in loss of pancreatic function. Exocrine insufficiency can lead to steatorrhoea, malnutrition, abdominal discomfort and weight loss. Endocrine insufficiency results in diabetes. CP thereby also leads to substantial impairment in quality of life for most patients (Pezzilli 2005; Wehler 2004).

Description of the intervention

Antioxidant supplements have been suggested as potentially useful treatment for pain in CP. Antioxidants are man-made and natural substances that can inhibit the production of free radicals or can bind and inactivate them (Feng 2010). Examples of antioxidants include vitamin C, vitamin A, vitamin E, glutathione, flavonoids (in tea, cocoa and several fruits and vegetables), superoxide dismutase and various peroxidases. Free radicals are associated with many deleterious effects as a result of their chemical reactivity. Unbound, they can cause damage to all cellular macromolecules, including proteins, carbohydrates, lipids and nucleic acids (Ramos-Márquez 2008). Epidemiological studies have reported that antioxidants may have both anti-inflammatory and anticarcinogenic effects (Owen 2000; Sala 2002). Furthermore, some researchers suggest that intake of natural antioxidants reduces the risks of cancer, coronary heart disease, diabetes and Alzheimer's disease (Temple 2000; Willett 2002). In general, antioxidants are associated with few (direct) adverse effects, especially when doses are low (e.g. comparable normal diet intake). With high-dose supplementation, headaches and gastrointestinal discomfort have been reported (Bhardwaj 2009; Bilton 1994a). However, over the long term, not all reports on the use of antioxidants are positive; for example, a recent Cochrane review comparing antioxidants versus placebo found that long-term prophylactic use of some antioxidants like beta carotene, vitamin A and vitamin E may even increase mortality (Bjelakovic 2008). Other antioxidants were not associated with this effect (Bjelakovic 2008). Therefore, thorough evaluation is needed before antioxidants can be implemented as standard of care.

How the intervention might work

Studies have shown that patients with CP have a significantly lower level of circulating antioxidants and increased free radical activity compared with healthy controls (Bowrey 1999; Guyan 1990; Kalvaria 1986). Reduced intake of antioxidants and postprandial pain along with reduced resorption due to malabsorption caused by exocrine pancreatic insufficiency are probable causes of decreased antioxidant status in patients with CP (Bhardwaj 2004; Rose 1986). Improving the status of antioxidants might reduce antioxidant stress and provide a way to ameliorate the disease process while reducing pain in CP (Witt 2007).

Why it is important to do this review

No satisfactory treatment for pain in CP is available. Non-opioid analgesics fail to relieve pain in many patients. Opioid analgesics are associated with many complications, like somnolence, obstipation and nausea, and present a serious risk of dependency. Antioxidants could be a promising alternative treatment that may relieve pain, improve health status and enhance quality of life in patients with CP. In contrast, potential harms of antioxidants should be thoroughly evaluated as well. This review aims to evaluate available evidence for both benefits and harms associated with the use of antioxidants in patients with CP.

OBJECTIVES

To assess the benefits and harms of antioxidants for the treatment of pain in patients with CP.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) evaluating antioxidants for treatment of pain in CP. Trials were included irrespective of blinding, numbers of participants randomly assigned or language of publication. Quasi-randomised trials were excluded.

Types of participants

We included all adult patients with established CP according to the criteria of at least one international guideline (Schneider 2007). Patients must have had some degree of pain, described as constant pain or as recurrent pain attacks.

Types of interventions

Trials with any of the following comparisons were included without restriction of dose, frequency, intensity, duration or route of administration.

- Trials comparing any antioxidant regimen, single or compound, versus placebo.
- Trials comparing different antioxidant regimens versus each other.
- Trials comparing any antioxidant regimen versus any other control intervention.

The following definitions for the different treatment modalities were used.

- Antioxidant: any medicinal product that inhibits the production of free radicals, or binds and inactivates them.
- Single antioxidant: use of only one antioxidant product during the study period.
- Combination antioxidants: use of more than one antioxidant product during the study period.
- Other control intervention: any substance or intervention that may have a pharmacological effect and is used as a control.

Types of outcome measures

Primary outcomes

- Pain: pain complaints after the intervention compared with before the intervention. Pain is a subjective outcome, and many different ways of measuring pain are used; therefore, no strict definition of pain can be provided. The pain outcome measures used in all trials are presented in a matrix table (Table 1).

Secondary outcomes

- Mortality.
- Adverse effects, including nausea, constipation, allergic reaction or any other as reported.. Adverse effects were classified as minor (e.g. headache, gastrointestinal intolerance) and major complications (e.g. allergic reactions).
- Pain medication: need for use of (additional) analgesic with no restriction on type of analgesic used.
- Quality of life.
- Number of admissions and duration of hospital stay during trial period.
- Number of pancreatitis events.
- Number of lost workdays.
- Antioxidant status measures: dependent on the antioxidant marker reported by trial authors.

Search methods for identification of studies

Electronic searches

The following databases were searched.

- Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1).
- MEDLINE via OVID (from 1950 to present) (Appendix 2).
- EMBASE via OVID (from 1980 to present) (Appendix 3).
- Conference Proceedings Citation Index-Science (CPCI-S) (from 1990 to present) (Appendix 4).

We developed these search strategies in cooperation with the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group (see Acknowledgements).

Searching other resources

A cross-reference search was performed of all included randomised trials and relevant reviews identified during the search process.

Data collection and analysis

This review was conducted according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

Selection of studies

Titles and abstracts were screened by two review authors independently. All potentially relevant hits were selected. In case of any uncertainty, hits were selected as well. Selection based on full text was performed by two review authors according to inclusion criteria. Disagreements were resolved by discussion. Excluded studies and reasons for exclusion are provided in the Characteristics of excluded studies table.

Data extraction and management

Two review authors independently extracted all relevant data. For each trial, participant characteristics, trial characteristics, data needed for methodological quality assessment of the trial and primary and secondary outcome measures were extracted according to availability. Data regarding participant characteristics included number of participants in each group, age and gender of participants, duration and etiology of disease, alcohol use, smoking and need for analgesic at baseline. Data regarding trial characteristics

included study design, sample size calculation, inclusion and exclusion criteria of the trial, follow-up period, loss to follow-up and information regarding antioxidant supplements. The latter included the type of antioxidant supplement used, the duration of treatment and the timing of outcome assessment.

Assessment of risk of bias in included studies

Based on available empirical evidence and the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*, we assessed the methodological quality of RCTs by using the tool for assessing risk of bias (Higgins 2008; Kjaergard 2001; Moher 1998; Schulz 1995). The following definitions were used for items assessed by this tool.

Sequence allocation

- Adequate: if the allocation sequence was generated by a computer or a random number table. Drawing lots, tossing a coin, shuffling cards and throwing dice were considered adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear: if the trial was described as randomised, but the method used for generation of the allocation sequence was not described.
- Inadequate: if a system involving dates, names or alternating allocation was used for allocation of participants.

Allocation concealment

- Adequate; if allocation of participants involved a central independent unit, an on-site locked computer or sealed envelopes.
- Unclear: if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate: if the allocation sequence was known to the investigators who assigned participants.

Blinding

- Adequate: if the trial was described (at least) as blind to participants or assessors and the method of blinding was described.
- Unclear: if the trial was described as (double) blind, but the method of blinding was not described.
- Inadequate: if the trial was not blinded.

Incomplete data outcome

- Adequate: if the percentage of dropouts did not exceed 20%, and numbers of and reasons for dropouts and withdrawals in all intervention groups are described.
- Unclear: if the report gives the impression that no dropouts or withdrawals occurred, but this is not specifically stated.
- Inadequate: if the percentage of dropouts exceeds 20%, or the numbers of and reasons for dropouts and withdrawals are not described.

Selective outcome reporting

- Adequate: if it was clear that published reports include all expected outcomes, including those that were prespecified.
- Unclear: if insufficient information was provided to permit clear judgement of this aspect.
- Inadequate: if not all relevant outcomes and prespecified outcomes were reported, or if they were incompletely reported.

Other sources of bias

- Adequate: if the study appeared to be free of other sources of bias, with special attention to funding source and potential conflicts of interest.
- Unclear: if a risk of potentially important bias exists, but sufficient information to assess this bias was lacking.
- Inadequate: if one or more sources of potentially important bias could be identified in the study (e.g. extreme baseline imbalances, other imbalances in study design).

Cross-over trials

For cross-over trials, we have examined the following additional sources of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a).

- Suitability of the cross-over design.
- Whether a carry-over effect was present, and if first period data were presented.

These aspects are discussed and are noted under the heading 'Other sources of bias' when concerns are present in individual trials.

Measures of treatment effect

Statistical analyses of binary data were conducted using risk ratios (RRs). Trials with zero events in both arms were excluded from meta-analyses. As a robustness assessment, meta-analyses with zero event trials were performed using risk differences in a sensitivity analysis. For continuous outcomes, weighted mean differences (WMDs) were preferably used, but when different scales were used for the same outcome, we used the standardised mean difference (SMD) instead. When data were presented as medians with ranges, study authors were contacted and were asked to provide additional data. If data could not be retrieved, a sensitivity analysis imputing data for missing means and standard deviations (calculated from available medians and ranges) was performed as well (Hozo 2005).

Assessment of heterogeneity

Heterogeneity was calculated using the Higgins Chi^2 test, and inconsistency in study effects was quantified by I^2 (Higgins 2002). A Chi^2 test with a P value < 0.10 was considered to indicate the presence of heterogeneity, and an I^2 > 50% was considered to suggest marked inconsistency in effect between studies.

Assessment of reporting biases

Funnel plots were used to provide a visual assessment of whether treatment estimates were associated with study size. These depictions may reveal the presence of publication or other types of bias (Begg 1994; Egger 1997; Macaskill 2001).

Data synthesis

Parallel trials

The inverse variance and Mantel-Haenzel methods were used for continuous and dichotomous outcomes, respectively.

Cross-over trials

For continuous outcomes, the generic inverse variance method using mean differences and standard errors from paired analysis was used for meta-analysis. If no paired data were available, we refrained from pooling data from cross-over trials. In these cases, we performed a sensitivity analysis by combining parallel and cross-over trials using unpaired data, as outlined below.

For dichotomous outcomes, the literature suggests that paired and unpaired analyses can be suitable for meta-analysis (Curtin 2002; Elbourne 2002). Both types of analysis yield similar effect estimates, but the unpaired analysis yields a wider confidence interval (a more conservative estimate). If possible, we adjusted the variance using the Becker and Balagtas method (Elbourne 2002; Stedman 2011). Advantages of this approach are that values are easily calculated and this method allows for combinations of cross-over and parallel trials while harnessing the power of cross-over studies. The disadvantage is that this approach requires reporting of additional data, which might not be available. If such data were not available, an unpaired analysis was performed.

Combining parallel and cross-over trials

When paired data from cross-over trials were available, we combined these with data from parallel trials using the general inverse variance method. Paired data from cross-over trials were entered into this model directly. For parallel trials, mean difference and standard error (calculated from the 95% confidence interval (CI)) were used for this purpose.

If no paired data were available, we performed a sensitivity analysis by combining unpaired data from cross-over trials with data from parallel trials. For this approach, the usual methods of meta-analysis were used.

For all meta-analyses, the fixed-effect model was used if no heterogeneity was present (Chi^2 P value > 0.1 and I^2 < 50%), or the random-effects model was used. Statistical analysis was conducted using the statistical package RevMan v.5.2.5, as provided by The Cochrane Collaboration (RevMan 2014).

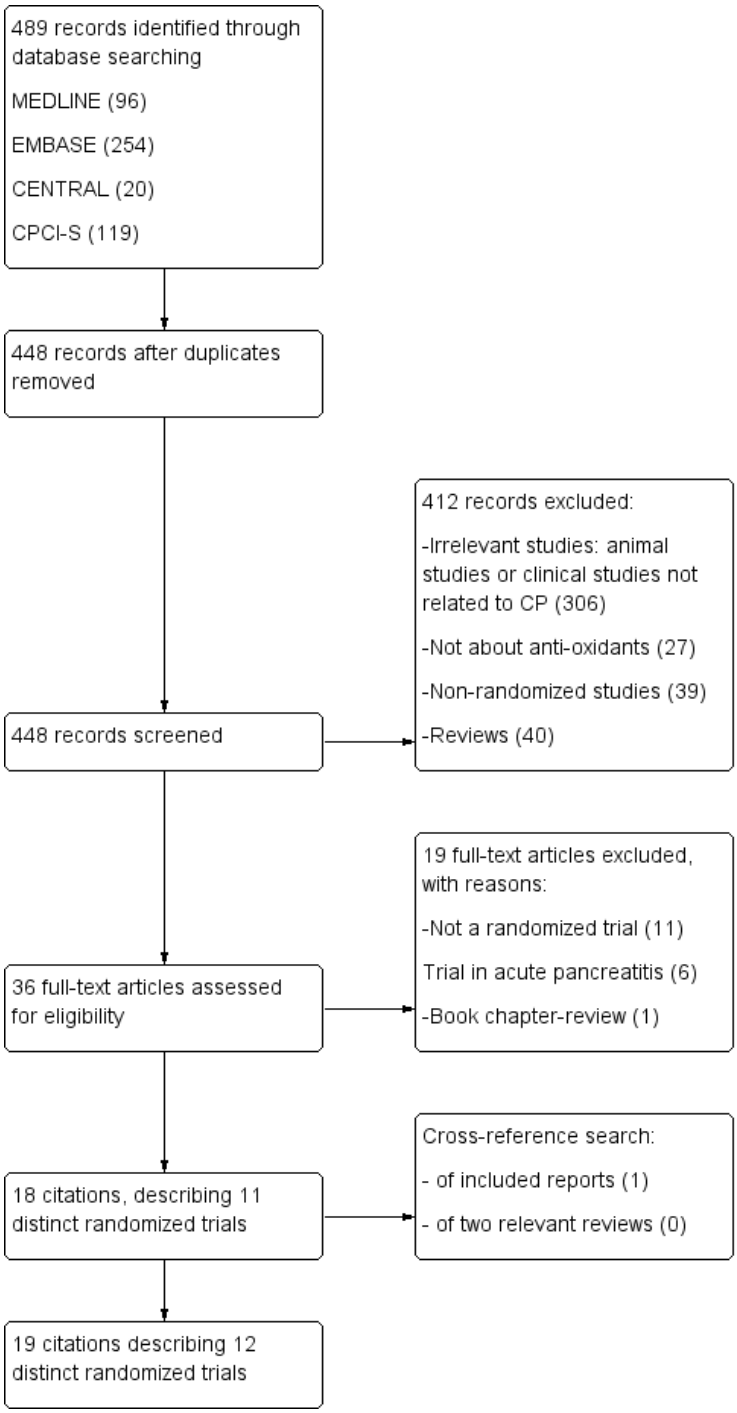
RESULTS

Description of studies

Results of the search

We performed the search on 16 October 2012 and obtained a total of 489 citations. Upon selection, we found a total of 19 eligible citations describing 11 distinct RCTs (Figure 1). All studies excluded after the first selection are listed along with reasons for exclusion in the Characteristics of excluded studies table. Cross-reference searching of all included randomised trials revealed one additional potentially eligible article (Nandi 2002). Cross-reference searching of two relevant reviews (Bjelakovic 2008; Monfared 2009) yielded no further eligible articles. Therefore, a total of 20 citations describing 12 distinct trials were included. By means of personal communication, we identified one ongoing trial, EUROPAC-2. Details of this trial are described in the Characteristics of ongoing studies table.

Figure 1. Study flow diagram.



Included studies

Eight of the 12 included trials were double-blind, placebo-controlled trials, and one trial was single-blinded (Durgaprasad 2005). Six trials used a cross-over design, and six a parallel-group design. Two trials were published only in abstract form (Deprez 2003; Nandi 2002). Trial sizes varied from 14 to 147 participants. Three trials (Bilton 1994a; Bilton 1994b; Uden 1990) included only participants with recurrent pancreatitis of non-gallstone origin (mostly alcohol). Durgaprasad 2005 excluded patients with alcoholic CP, and Kirk 2006 excluded patients with CP who had gallstones. The other trials included participants with established CP of all etiologies. Trials used a variety of antioxidants and reported on various outcomes. Most trials assessed pain using a visual analogue scale (VAS) (Hawker 2011); however different scales and methods of reporting were used (Table 1).

Eleven of the 12 included trials described the effects of antioxidants on chronic abdominal pain in CP. One trial (Salim 1991) evaluated the effects of antioxidants on acute pain during exacerbations of CP. As this is a different indication, results of this trial are described separately.

Ten trials compared antioxidant treatment versus placebo. Deprez 2003 compared antioxidants with dietary counselling versus dietary counselling alone but published no data that were suitable for meta-analysis. Jarosz 2010 compared antioxidants versus no intervention (standard treatment). Given the availability of data, we performed only one of the three comparisons we had set out to perform (i.e. antioxidants vs placebo/no intervention).

Further characteristics of included trials are described in the Characteristics of included studies table. Baseline characteristics of included participants are described in Table 2.

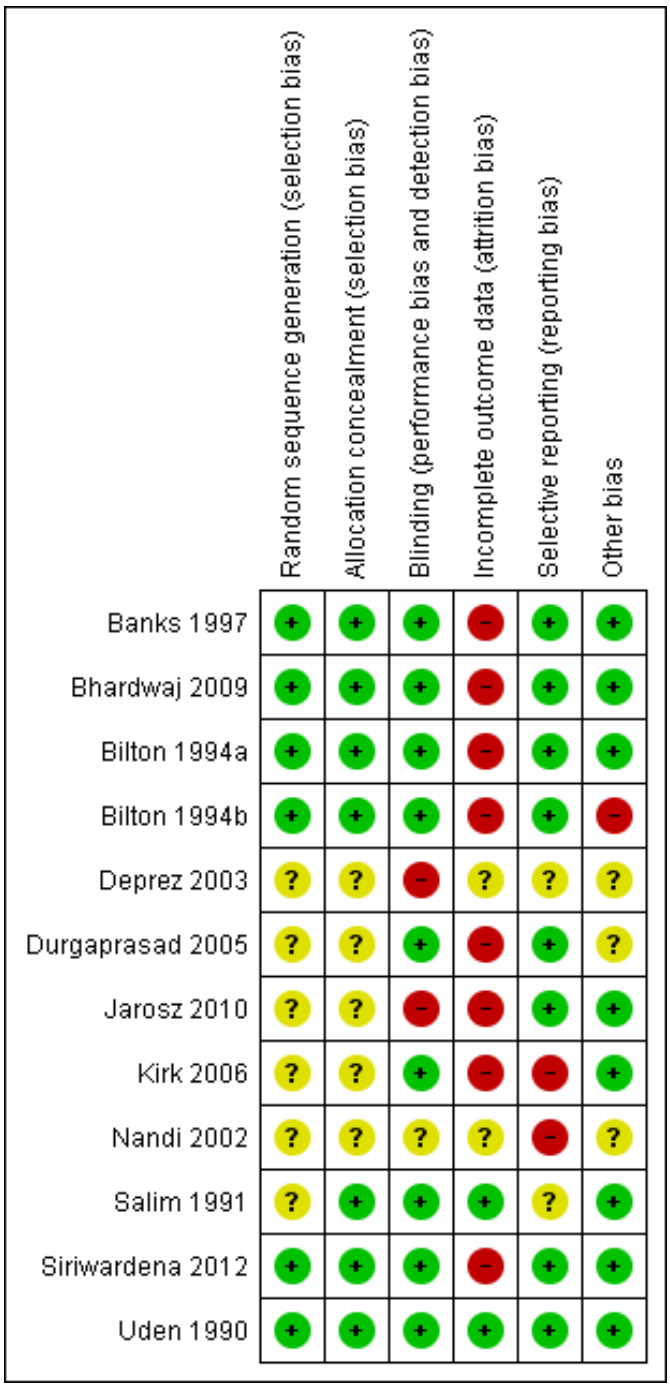
Excluded studies

Reports excluded after initial screening of titles and abstracts are listed along with reasons for exclusion in the Characteristics of excluded studies table.

Risk of bias in included studies

A risk of bias summary table of included trials is presented in Figure 2. The most common weakness of included trials was that outcome data were incomplete (high dropout rates, see below). Regarding other items, a division can be made between well-conducted trials with relatively low risk of bias (Banks 1997; Bhardwaj 2009; Bilton 1994a; Bilton 1994b; Siriwardena 2012; Uden 1990) and poorly conducted trials with higher risk of bias.

Figure 2. Summary of risk of bias: review authors' judgements about each risk of bias domain for included trials.



Dropout rates

The dropout rates of individual trials, the distribution of dropouts among trials arms and the reasons for dropout are stated in the 'Risk of bias table' sections of the Characteristics of included studies. In the studies Bilton 1994a and Bilton 1994b, most dropouts were in the antioxidant arms and most cases of dropout were due to adverse events. In all other trials, dropouts were similarly divided between trial arms.

Cross-over trials

Appropriateness of the cross-over design

CP is a chronic condition, making it a good candidate for cross-over trials. The major outcomes of these studies (i.e. pain, quality of life, antioxidant levels, number of pancreatitis attacks) are reversible outcomes, which are suitable for this design. Antioxidant supplementation is a reversible treatment, and its effects are generally short-lasting. However, two facts need to be noted: (1) Some antioxidants (e.g. vitamin E) are fat soluble, allowing for long-term storage (in contrast to water-soluble antioxidants, which are excreted immediately). This might result in some carry-over effect if levels remain high in the second period; and (2) the mechanisms by which antioxidants might work in CP are not entirely elucidated. Although the major hypothessed action is reversible (i.e. countering the high free radical state in CP), it cannot be ruled out that some mechanisms might have longer-lasting effects. Therefore, empirical data from these trials must be evaluated to rule out any carry-over effect.

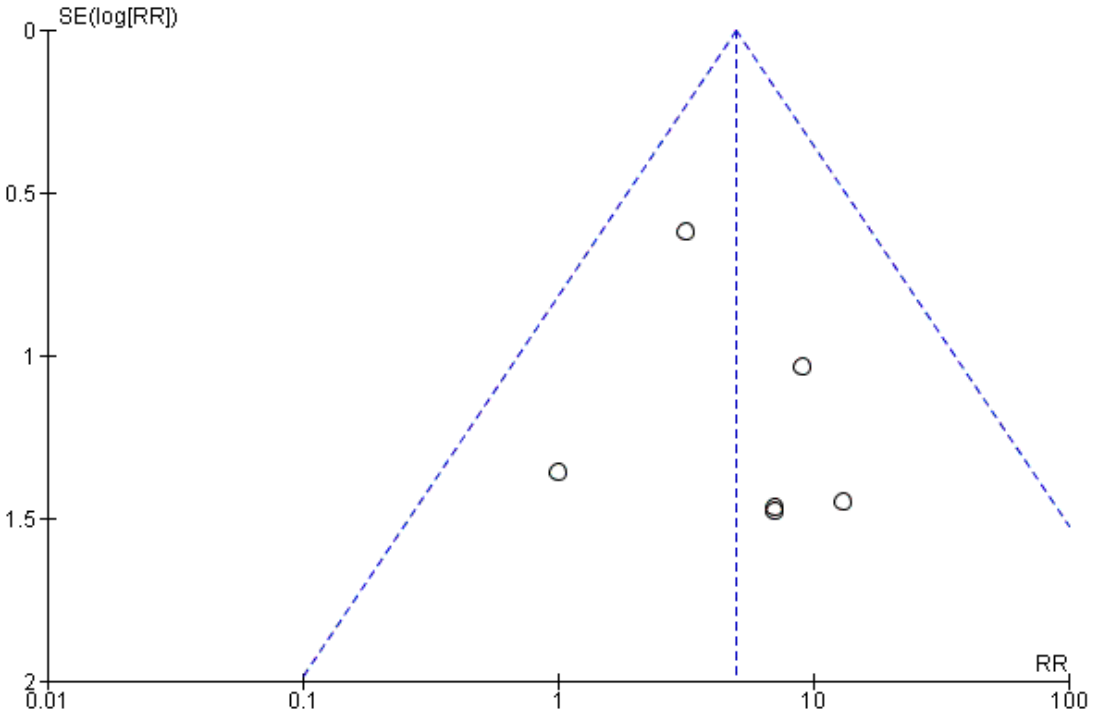
Carry-over effect

Published reports of all cross-over trials, except Deprez 2003 (published as abstract only), discussed the risk of carry-over effect. Both Uden 1990 and Banks 1997 statistically investigated the presence of carry-over effect and stated that they did not identify a significant carry-over effect in clinical or biochemical outcomes. Uden 1990 used the fat-soluble vitamin E, and its levels showed no signs of a carry-over effect at the end of the second study period. Bilton 1994a and Bilton 1994b describe the analysis performed by Uden 1990 because these trials were performed by the same group. Kirk 2006 showed that biochemically the levels of fat-soluble vitamin E tended to remain slightly elevated until the end of the study. These study authors identify this as a potential limitation of the study but conclude that it would have resulted in a bias towards the zero (no) effect, although this study showed a significant difference in clinical outcome. Based on these results, we can conclude that empirical evidence shows that the carry-over effect does not play an important role in this comparison.

Publication bias

Publication bias was evaluated by means of funnels plots, but no clear evidence of such bias was observed (Figure 3).

Figure 3. Evaluation of publication bias by funnel plot (based on the outcome 'adverse effects').



Effects of interventions

See: **Summary of findings for the main comparison** Antioxidant versus control intervention for pain in chronic pancreatitis

Effects of antioxidants on chronic pain in chronic pancreatitis

Primary outcome-pain

An overview of the results of different pain outcome measures reported by the included trials is presented in Table 3.

Eight trials assessed pain using a VAS score (Table 1). Not all data were suitable for meta-analysis. Bilton 1994a and Bilton 1994b reported that no significant difference was noted but did not provide any data. Kirk 2006 excluded the VAS score from analysis because of poor reporting by participants. Deprez 2003 reported only baseline VAS scores.

Pain VAS scores from two cross-over trials were pooled (Analysis 1.1), showing a significant reduction in pain VAS scores in favour of the antioxidant group (MD -0.34 VAS points, 95% CI -0.67 to -0.01, P value 0.04) (Analysis 1.1). Two trials with a parallel-group design were pooled, showing no difference in pain levels (MD -0.26, 95% CI -1.07 to 0.56, P value 0.5) (Analysis 1.2). When results of all trials were combined (118 participants), a significant reduction in VAS score was observed in the antioxidant groups (MD -0.33, 95% CI -0.64 to -0.02, P value 0.04) (Analysis 1.3). Three parallel trials reported the proportion of pain-free participants as an outcome measure. Meta-analysis showed a non-statistically significant difference between groups (RR 1.73, 95% CI 0.95 to 3.15, P value 0.07) (Analysis 1.4).

Secondary outcomes

Adverse effects and mortality

Eight trials reported adverse effects. In total, 33 of 208 (16%) adverse events were reported in the antioxidant group compared with five of 196 (3%) in the placebo group. Separate analysis of cross-over trials (RR 5.80, 95% CI 1.56 to 21.53, P value 0.009) and parallel trials (RR 4.43, 95% CI 1.60 to 12.29, P value 0.004) showed significantly higher adverse events in the antioxidant group (Analysis 1.5). Analysis of cross-over trials was based on unpaired data because reported data did not allow for correction of variance. Sensitivity analyses combining cross-over and parallel trials

(Analysis 1.6) and data for zero event trials using risk differences produced similar results (Analysis 1.7). Most reported adverse events were minor complications and included headache, gastrointestinal intolerance, obstipation and nausea. Only two moderate to severe adverse effects were described. Banks 1997 reported that one participant developed swelling of joints, a rash and a puffy face. Siriwardena 2012 described one participant in the antioxidant group who developed convulsions as the result of hepatic encephalopathy, although the relation of this to antioxidant treatment was uncertain. No trials reported any mortality.

Pain medication

Three trials including 210 participants reported on the need for pain medication during the study period. Data appeared unsuitable for meta-analysis. Banks 1997 showed no difference in the need for morphine use between participants given antioxidants and those given placebo (increase of 5.5%, range -49% to +129%). Bhardwaj 2009 reported a positive effect of antioxidants compared with placebo when evaluating the numbers of oral analgesic tablets required per month (MD -6.15, 95% CI -2.65 to -9.65). Similar results were found for the numbers of analgesic injections required per month after adjustment for baseline differences (MD -0.44, 95% CI -0.07 to -0.81). Siriwardena 2012 described no difference in the need for opioid analgesic when antioxidants were used (MD -13.7 mg/d, 95% CI -38.0 to 10.6).

Quality of life

Three trials including 102 participants reported on quality of life. Data were unsuitable for meta-analysis. Banks 1997 reported on activities of daily living and described no differences between antioxidants and placebo (MD -3.3, 95% CI -10.3 to 3.7, P value 0.32). Kirk 2006 assessed quality of life using the 36-Item Short Form Health Survey (SF-36) questionnaire. Results were presented for nine components separately. Six of the quality of life components (physical function, physical role, social function, pain, health perception and change in health) showed significant improvement in the antioxidant group compared with the placebo group. Siriwardena 2012 examined quality of life using four different quality of life questionnaires. None revealed a significant difference.

Admissions and duration of hospital stay

Two trials including 197 participants reported on this outcome. Bhardwaj 2009 reported on the need for hospitalisation. A small difference was observed in favour of antioxidant use after adjustment for baseline values (MD -0.034, 95% CI -0.069 to -0.002). Siriwardena 2012 showed no differences between study groups (MD -0.06, 95% CI -3.80 to 3.53).

Number of attacks of pancreatitis

Three cross-over trials including 54 participants reported the frequency of severe attacks of pancreatic pain. Fifteen attacks occurred: five in the antioxidant period and 10 in the placebo period. This difference was not statistically significant (Analysis 1.8). This analysis was based on unpaired data, as reported data did not allow for correction of variance.

Loss of workdays

Only Bhardwaj 2009 (127 participants) reported on the number of workdays lost. This trial reported a favourable larger decrease in workdays lost in the antioxidant group compared with the placebo group (11.4 (SD 9.1) vs 7.6 (SD 7.2), P value 0.014).

Antioxidant level measures

Most studies reported several measures of antioxidant status. Four of these measures were reported by three or more trials and were chosen for meta-analysis (i.e. vitamin C and A, selenium and beta-carotene). All cross-trials reported unpaired data for this outcome and could be included only in sensitivity analyses. Main meta-analyses based on parallel trials showed significantly higher levels of vitamins C and E in the antioxidant groups (Analysis 1.9; Analysis 1.11). Sensitivity analysis of these outcomes confirmed these findings (Analysis 1.10; Analysis 1.12). Finallly, sensitivity analysis of selenium and beta-carotene suggested higher levels in the antioxidant groups (Analysis 1.13; Analysis 1.14).

Effects of antioxidants on acute pain in chronic pancreatitis

Primary outcome-pain

Salim 1991 included patients with CP within two hours of onset of an acute pain episode. Participants were randomly assigned to three groups: two antioxidant groups (allopurinol and dimethylsulfoxide) and a placebo group. This trial assessed the proportions of pain-free participants in the three study groups at different moments during admission. After 12 hours of admission, the proportions of pain-free participants were significantly higher in the two antioxidant groups than in the placebo group (respectively, 13/22 (59%) and 12/21 (57%) vs 4/23 (17%); P value < 0.01). After 24 hours, all participants in the two antioxidant groups achieved pain relief versus 12 of 23 (52%) in the placebo group (P value < 0.01). Additionally, after two days, all participants in the placebo group experienced epigastric tenderness versus 12 of 22 (54%) in the allopurinol group and 11 of 21 (52%) in the dimethylsulfoxide group (P value < 0.01). After three days, only four of 22 (18%)

and three of 21 (14%) participants, respectively, in the allopurinol and dimethylsulfoxide groups, experienced epigastric tenderness, and 17 of 23 (74%) in the placebo group had epigastric tenderness (P value < 0.01).

Secondary outcomes

This trial reported on only two of the secondary outcome measures (i.e. adverse effects and hospital stay) (Salim 1991). Five (23%) participants in the allopurinol group experienced adverse effects, including allergic reactions (rash) and headaches. A total of four (19%) participants in the dimethylsulfoxide group experienced adverse effects (intolerance to medication (1×) and headache (3×)). None of the participants in the placebo group reported any adverse effects.

This trial also reported the proportions of participants discharged from hospital after three days. All participants in the allopurinol (n = 22) and dimethylsulfoxide (n = 21) groups were discharged home after three days compared with five of 23 (22%) in the placebo group (P value < 0.01).

DISCUSSION

Summary of main results

This systematic review shows several important findings regarding antioxidant treatment in chronic pancreatitis. First, it shows that antioxidant use may reduce pain in chronic pancreatitis. Second, it shows that antioxidant use is associated with adverse effects in 16% of patients. Although mostly mild in nature, these adverse effects sometimes result in discontinuation of antioxidant medication. Third, 12 randomised trials have been conducted, but these trials included small sample sizes, suffered high rates of dropout and were inadequate in reporting of outcomes critical for decision making.

Meta-analysis of pain VAS scores showed a significant reduction favouring antioxidant treatment. This result was based on the findings of four trials, three of which had adequate methodology for most items included in the risk of bias tool (Figure 2). The contribution of the fourth trial was limited (weight in the analysis was 3%). No heterogeneity was observed between studies (I^2 = 0%). All of these aspects increase the reliability of the findings. The marginal statistical significance (P value 0.04) on the other hand is probably an indication of the small numbers of included participants. The overall VAS score was only slightly reduced by antioxidants (0.33 of 10 points) (Analysis 1.3). Such a small difference is of unclear clinical relevance, and its clinical impact is uncertain.

A factor contributing to reported outcomes could be that most participants in the trials had only mild pain. (The pain VAS score under placebo treatment was around three points in most trials.) When the VAS pain score was higher, as in Durgaprasad 2005, the absolute reduction tended to be greater (e.g. a reduction of -0.76 from a placebo VAS of 6.57) (Analysis 1.2). The proportion of pain-free participants offers a more clinically relevant outcome. Our meta-analysis shows that the difference in this outcome was not statistically significant, although a trend favouring antioxidant treatment was observed (Analysis 1.4). It is clear that more evidence is needed to establish or reject potential differences.

Another important outcome for clinical practice is the adverse events observed in 16% of participants treated with antioxidants (Analysis 1.6). Although most adverse events were mild, trial authors reported that participants often decided to discontinue antioxidant treatment because of these events.

Other important secondary outcomes, such as use of pain medication, rate of exacerbation of pancreatitis and quality of life, were not well evaluated in the included trials, and data were insufficient to permit reliable conclusions. Future trials need to consider these outcomes and preferably present data in ways that facilitate meta-analysis, by reporting complete outcome data and choosing outcome measures comparable with those of previous studies.

Overall completeness and applicability of evidence

Inclusion criteria varied between trials. Some trials included only non-alcoholic participants with CP, and others recruited all patients with CP, including those with recurrent attacks of pancreatitis. This is representative of the heterogeneity of patients with CP and may justify an argument regarding the generalisability of the results of this review. A noteworthy aspect based on the hypothesised mechanism of antioxidant treatment is the duration of disease at the time of antioxidant therapy. Antioxidant therapy is hypothesised to reduce damage to the pancreas caused by oxidative stress. Maximal benefit is likely to be achieved when antioxidants are administered early in the disease process (before the damage has been done) and are continued for a substantial time. This aspect did not receive attention in the included trials. Only a few reported the duration of disease of included participants (Table 2), and none performed subgroup analysis based on this characteristic. The limited number of participants may have been a contributing factor in this regard.

Variation in reporting of outcome measures posed an important challenge for a summary of results (e.g. nearly all trials measured pain using a VAS score, but only four trials reported data that were suitable for meta-analysis). Contacting study authors was not helpful, as most trials were conducted more than 15 years ago and original data were no longer available. In two studies, trial authors stated only the absence of a significant difference without presenting data (Bilton 1994a; Bilton 1994b). This way of reporting should be avoided because pooling of trial data could expose differences in treatments not observed in single trials. These trials also used different types of antioxidant regimens, with variations

evident in types, numbers of preparations and doses of antioxidants used. Because of the small number of available trials, the influence of different regimens could not be evaluated in subgroups. Moreover, the lack of trials comparing different types of antioxidants makes direct comparison not feasible. Finally, only one trial studied the effects of antioxidants on acute pain in chronic pancreatitis. More evidence is needed before conclusions can be drawn.

Quality of the evidence

The 12 RCTs included a total of 585 participants. The most important limitation was the high rate of dropout due to adverse events or non-compliance. Six trials were relatively well conducted in terms of adequate randomisation, concealment of allocation, blinding and placebo control (Banks 1997; Bhardwaj 2009; Bilton 1994a; Bilton 1994b; Siriwardena 2012; Uden 1990), but the remaining trials had serious methodological flaws (Figure 2). Another important limitation was the small sample size of most trials. Eight of the included trials recruited fewer than 40 participants. This is to some extent attenuated by a cross-over design in some trials, in that this design allows more power than is attained by a parallel-group design. Still, most trials were underpowered to detect any differences in clinically important outcomes.

Potential biases in the review process

Inconsistent reporting posed the most important challenge to this systematic review. Two randomised trials (Deprez 2003; Nandi 2002) were published only as abstracts and did not contribute data on any of the comparisons. This kind of publication bias has been widely acknowledged to be problematic, but solutions such as trial registration have already led to progress in resolution of this problem (McGee 2011). Second, we were unable to obtain suitable data for several outcomes. This was due mainly to incomplete reporting of trial data and to the fact that most trials were conducted some time ago. Third, the cross-reference search identified one additional eligible report not identified by our electronic search. This report was published as an abstract in a supplement that was not indexed in any electronic database (Nandi 2002). This again shows that cross-reference searching of included trials is an important step in the search process. Fourth, the use of unpaired data might lead to underestimation of the true level of statistical heterogeneity owing to the inflation of confidence intervals (as a result of the more conservative estimation). Although this can affect results in general, for our review the impact is probably limited. Heterogeneity estimates were consistent for all outcomes between estimates from parallel trial analysis and those from sensitivity analysis, including unpaired data. For the only outcome with exclusively unpaired data from cross-over trials, heterogeneity was found to be significant, thus negating this potential bias. Finally, our search was conducted more than one year ago, meaning that some recent publications might have been missed. This lag is due to the fact that several steps in the process took more time than was anticipated. For practical reasons, we have planned an update of the review early next year, to keep results of this review recent and relevant.

Agreements and disagreements with other studies or reviews

A recent systematic review of antioxidant therapy in pancreatitis (Monfared 2009) was unable to provide clear conclusions about the benefit of antioxidant therapy and underlined the need for additional research. This review, however, included trials on both acute and chronic pancreatitis. These diseases were discussed simultaneously, and conclusions were not always clearly separated. Because of the distinct pathophysiological and clinical presentation of acute and chronic pancreatitis, combining trials on both diseases into a single analysis may be inappropriate. This review stratified the analysis per types of antioxidants used. Although this is a more precise approach, the lack of data for each type of antioxidant limits the possibility of useful conclusions. The fact that trials use various types of antioxidants indicates that clinicians are more interested in studying the hypothesis that reducing oxidative stress may improve health outcome than in evaluating which substance is more efficient. The review concluded that trials were heterogeneous and that drawing conclusions was impossible. The review authors stated that based on the results of the largest trial by Bhardwaj 2009, treatment with cocktails of oxidants could have a positive effect on pain reduction.

Another review (Braganza 2010) discussed the role of micronutrient therapy in CP and described the role of antioxidants as part of the review. This review concluded that antioxidants can control background pain and can curb acute attacks in chronic pancreatitis. A drawback of the Braganza 2010 review is the lack of assessment of risk of bias of the included trials. Moreover, since time of the Braganza review, two new trials have been published, which were not included in that review. Finally, both of the reviews discussed here (Braganza 2010; Monfared 2009) lacked quantitative assessment of various important outcomes, especially adverse events, although these data were available.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence shows that antioxidants can reduce pain slightly in patients with CP, but the clinical relevance of the small observed difference is uncertain. With such small effects, routine use of antioxidants is questionable. In a minority of patients, the use of antioxidants can lead to mild adverse effects (headache and gastrointestinal intolerance), which can mandate cessation of treatment.

Effects of antioxidants on other outcomes are still largely uncertain because of lack of data. Antioxidants also seem to benefit patients with CP during acute abdominal pain episodes (exacerbations), although evidence is insufficient for reliable conclusions.

Implications for research

Topics that have not been sufficiently evaluated include:

- providing additional data on the effects of antioxidants on pain, especially in terms of outcomes with clear clinical relevance, such as becoming pain free;
- clarifying the effects of antioxidants on secondary outcomes such as quality of life and rate of pancreatitis flare-ups; and
- studying whether the timing of intervention (early intervention) can affect the outcome of antioxidant treatment.

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REFERENCES

References to studies included in this review

Banks 1997 *{published data only}*
Banks PA, Hughes M, Ferrante M, Noordhoek EC, Ramagopal V, Slivka A. Does allopurinol reduce pain of chronic pancreatitis?. *International Journal of Pancreatology* 1997;**22**(3):171–6.

Bhardwaj 2009 *{published data only}*
* Bhardwaj P, Garg PK, Maulik SK, Saraya A, Tandon RK, Acharya SK. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009;**136**(1):149–59.
Bhardwaj P, Garg PK, Saraya A, Acharya S. Antioxidant supplementation for pain relief in chronic pancreatitis: a randomized placebo controlled double blind trial. *Gastroenterology* 2007;**132**:A51.
Bhardwaj PG. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009;**136**:abstract.

Bilton 1994a *{published data only}*
Bilton D, Schofield D, Mei G, Kay PM, Bottiglieri T, Braganza JM. Placebo-controlled trials of antioxidant therapy including S-adenosylmethionine in patients with recurrent non-gallstone pancreatitis. *Clinical Drug Investigation* 1994;**8**:10–20.

Bilton 1994b *{published data only}*
Bilton D, Schofield D, Mei G, Kay PM, Bottiglieri T, Braganza JM. Placebo-controlled trials of antioxidant therapy including S-adenosylmethionine in patients with recurrent non-gallstone pancreatitis. *Clinical Drug Investigation* 1994;**8**:10–20.

Deprez 2003 *{published data only}*
Deprez PH, Delazzer E, Galanti L, Lebrun J, Geubel A, Horsmans Y. Clinical and nutritional effects of antioxidant supplementation: a prospective randomized study in patients with chronic pancreatitis. *Gastroenterology* 2003; **124**(4):A90.

Durgaprasad 2005 *{published data only}*
Durgaprasad S, Pai CG, Vasanthkumar, Alvres JF, Namitha S. A pilot study of the antioxidant effect of curcumin in tropical pancreatitis. *Indian Journal of Medical Research* 2005;**122**(4):315–8.

Jarosz 2010 *{published data only}*
Jarosz M, Orzeszko M, Rychlik E, Kozuch M. Antioxidants in the treatment of chronic pancreatis [Antyoksydanty w leczeniu przewlek ł ego zapalenia trzustki]. *Gastroenterologia Polska* 2010;**17**:41–6.

Kirk 2006 *{published data only}*
Kirk GR, White JS, McKie L, Stevenson M, Young I, Clements WD, Rowlands BJ. Combined antioxidant therapy reduces pain and improves quality of life in chronic pancreatitis. *Journal of Gastrointestinal Surgery* 2006;**10**(4): 499–503.

Nandi 2002 *{published data only}*
Nandi B, Garg PK, Bhardwaj P, Prakash S, Tandon RK. Efficacy of antioxidants for pain relief in patients with chronic pancreatitis: a randomized controlled trial. *Indian Journal of Gastroenterology* 2002;**21**(Suppl 1):A43.

Salim 1991 *{published data only}*
Salim AS. Role of oxygen-derived free radical scavengers in the treatment of recurrent pain produced by chronic pancreatitis. A new approach.. *Archives of Surgery* 1991;**9**: 1109–14.

Siriwardena 2012 *{published data only}*
Shah N, Mason JM, Makin AJ, Sheen AJ, Siriwardena AK. A randomised, double-blind, placebo-controlled trial of oral antioxidant therapy for chronic pancreatitis: the final results of the ANTICIPATE study. *British Journal of Surgery* 2012; **99**:2.
Siriwardena A, Mason J, Sheen A, Makin A, Shah N. Antioxidant therapy for chronic pancreatitis: the final

results of a randomised, double blind, placebo-controlled trial (the ANTICIPATE STUDY). *HPB* 2012;**14**:663.
Siriwardena AK, Mason JM, Shah NS, Sheen AJ. Antioxidant therapy for chronic pancreatitis: a randomized, controlled trial. *Gastroenterology* 2012;**142**:S113.
* Siriwardena AK, Mason JM, Sheen AJ, Makin AJ, Shah NS. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. *Gastroenterology* 2012;**143**:655-63.

Uden 1990 ***{published data only}***
Uden S, Bilton D, Nathan L, Hunt LP, Main C, Braganza JM. Antioxidant therapy for recurrent pancreatitis: placebo-controlled trial. *Alimentary Pharmacology & Therapeutics* 1990;**4**(4):357–71.
Uden S, Main C. Placebo-controlled double-blind trial of antioxidant supplements in patients with recurrent pancreatitis. *Clinical Science* 1989;**77**(Suppl 21):26P–27P.
Uden S, Schofield D, Miller PF, Day JP, Bottiglier T, Braganza JM. Antioxidant therapy for recurrent pancreatitis: biochemical profiles in a placebo-controlled trial. *Alimentary Pharmacology & Therapeutics* 1992;**6**(2):229–40.

References to studies excluded from this review

Bagul 2006 ***{published data only}***
Bagul A, Siriwardena AK. Long-term outcome of oral anti-oxidant therapy in patients with painful chronic pancreatitis. *Gastroenterology* 2006;**130**(4):A517.

Bhardwaj 2004 ***{published data only}***
Bhardwaj P, Thareja S, Prakash S, Saraya A, Bhardwaj P, Thareja S, et al. Micronutrient antioxidant intake in patients with chronic pancreatitis. *Tropical Gastroenterology* 2004;**25**:69–72.

Bhardwaj 2006 ***{published data only}***
Bhardwaj P, Garg PK, Saraya A. Free radical mediated oxidative stress and antioxidant status in patients with chronic pancreatitis. *Free Radical Research* 2006;**40**:S107.

Braganza 1991 ***{published data only}***
Braganza JM. Antioxidant therapy for pancreatitis-clinical experience. *Pathogenesis of Pancreatitis*. Manchester, UK: Manchester University Press, 1991:178–97.

De las Heras 2000 ***{published data only}***
De las Heras CG, Garcia de la Paz A, Fernandez MD, Fernandez-Forcelledo JL. Use of antioxidants to treat pain in chronic pancreatitis. *Revista Espanola de Enfermedades Digestivas* 2000;**92**:375–85.

Klapdor 2012 ***{published data only}***
Klapdor S, Richter E, Klapdor R. Vitamin D status and per-oral vitamin D supplementation in patients suffering from chronic pancreatitis and pancreatic cancer disease. *Anticancer Research* 2012;**32**:1991–8.

Martinez-Torres 2009 ***{published data only}***
Martinez-Torres HR-L. Oral allopurinol to prevent hyperamylasemia and acute pancreatitis after endoscopic retrograde cholangiopancreatography. *World Journal of Gastroenterology* 2009;**15**:7.

Matthew 1996 ***{published data only}***
Mathew P, Wyllie R, Van LF, Steffen RM, Kay MH, Mathew P, et al. Antioxidants in hereditary pancreatitis. *American Journal of Gastroenterology* 1996;**91**:1558–62.

Milnerowicz 2005 ***{published data only}***
Milnerowicz H, Jablonowska M, Milnerowicz S. The level of GSH and antioxidant enzyme activity: GPx and Cu/Zn SOD in patients with pancreatitis. *FEBS Journal* 2005;**272**: 427.

Mosler 2005 ***{published data only}***
Mosler P, Sherman S, Marks J, Watkins JL, Geenen JE, Jamidar P, et al. Does prophylactic allopurinol administration reduce the risk and severity of post-ERCP pancreatitis: randomized prospective multicenter study. *Gastrointestinal Endoscopy* 2005;**61**:AB100.

Nakamura 1996 ***{published data only}***
Nakamura T, Takebe K, Imamura K, Tando Y, Yamada N, Arai Y, et al. Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). *Acta Gastro-enterologica Belgica* 1996;**59**:10–4.

Romagnuolo 2008 ***{published data only}***
* Romagnuolo J, Hilsden R, Sandha GS, Cole M, Bass S, May G, et al. Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography: a randomized placebo-controlled trial. *Clinical Gastroenterology and Hepatology* 2008;**6**:465–71.
Romagnuolo J, Hilsden RJ, Sandha GS, Cole MJ, Bass S, May GR, et al. Allopurinol to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP): a randomized placebo-controlled trial. *Gastrointestinal Endoscopy* 2008;**67**:AB328.
Romagnuolo J, Sandha G, Kruger C, May G, Cole N, Bass S, et al. Allopurinol to prevent post-ERCP pancreatitis: blind interim analysis of a randomized placebo-controlled trial. *Gastrointestinal Endoscopy* 2005;**61**:AB195.

Shah 2010 ***{published data only}***
Shah NS, Makin AJ, Sheen AJ, Siriwardena AK. Quality of life assessment in patients with chronic pancreatitis receiving antioxidant therapy. *World Journal of Gastroenterology* 2010; **16**:4066–71.

Shalimar 2011 ***{published data only}***
Shalimar S, Midha S, Bhardwaj P, Garg PK. Long-term pain relief with optimized medical therapy including antioxidants in patients with chronic pancreatitis. *Gastroenterology* 2011; **140**:S547.

Sinwardena 2006 ***{published data only}***
Sinwardena AK, Mason JM, Balachandra S, Bagul A, Galloway S, Formela L, et al. Randomized, double-blind, placebo-controlled, trial of high-dose intravenous anti-oxidant therapy in severe acute pancreatitis. *Gastroenterology* 2006;**130**:A83.

Uden 1988 ***{published data only}***
Uden S, Acheson DW, Reeves J, Worthington HV, Hunt LP, Brown S, et al. Antioxidants, enzyme induction, and chronic pancreatitis: a reappraisal following studies in

patients on anticonvulsants. *European Journal of Clinical Nutrition* 1988;**42**:561–9.

References to ongoing studies

EUROPAC-2 ***{published data only}***

EUROPAC-2.- Pain Treatment of Hereditary and Idiopathic Pancreatitis. Clinicaltrials.gov.

Additional references

Apte 1999

Apte MV, Keogh GW, Wilson JS. Chronic pancreatitis: complications and management. *Journal of Clinical Gastroenterology* 1999;**29**(3):225–40.

Begg 1994

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**(4): 1088–101. [PUBMED: 7786990]

Bjelakovic 2008

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for preventing gastrointestinal cancers. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD004183.pub3]

Bowrey 1999

Bowrey DJ, Morris-Stiff GJ, Puntis MC. Selenium deficiency and chronic pancreatitis: disease mechanism and potential for therapy. *HPB Surgery* 1999;**11**(4):207–15.

Braganza 2010

Braganza JM, Dormandy TL. Micronutrient therapy for chronic pancreatitis: rationale and impact. *Journal of the Pancreas* 2010;**11**(2):99–112.

Curtin 2002

Curtin F, Elbourne D, Altman DG. Meta-analysis combining parallel and cross-over clinical trials. II: Binary outcomes. *Statistics in Medicine* 2002;**21**(15):2145–59.

Dite 2001

Dite P, Stary K, Novotny I, Precechtelova M, Dolina J, Lata J, Zboril V. Incidence of chronic pancreatitis in the Czech Republic. *The European Journal of Gastroenterology and Hepatology* 2001;**13**:749–50.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Feng 2010

Feng Z, Liu Z, Li X, Jia H, Sun L, Tian C, et al. Alpha-tocopherol is an effective phase II enzyme inducer: protective effects on acrolein-induced oxidative stress and mitochondrial dysfunction in human retinal pigment epithelial cells. *The Journal of Nutritional Biochemistry* 2010;**21(12)**:1222–31.

Gachago 2008

Gachago C, Draganov PV. Pain management in chronic pancreatitis. *World Journal of Gastroenterology* 2008;**14**(20): 3137–48.

Guyan 1990

Guyan PM, Uden S, Braganza JM. Heightened free radical activity in pancreatitis. *Free Radical Biology and Medicine* 1990;**8**(4):347–54.

Hawker 2011

Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care and Research* 2011;**63**(Suppl 11):S240–52.

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

Higgins 2008

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Handbook for Systematic Reviews of Interventions*. New York: John Wiley & Sons Ltd, 2008.

Higgins 2008a

Higgins JPT, Green S. Section 16.4.3. Assessing risk of bias in cross-over trials. *Cochrane Handbook for Systematic Reviews of Interventions*. New York: John Wiley & Sons Ltd, 2008.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**(1):13.

Kalvaria 1986

Kalvaria I, Labadarios D, Shephard GS, Visser L, Marks IN. Biochemical vitamin E deficiency in chronic pancreatitis. *International Journal of Pancreatology* 1986;**1**(2):119–28.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomised trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**(11):982–9.

Levy 2006

Levy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. *Gastroenterology Clinical Biology* 2006;**30**:838–44.

Macaskill 2001

Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Statistics in Medicine* 2001;**20**:641–54.

McGee 2011
McGee RG, Su M, Kelly PJ, Higgins GY, Craig JC, Webster AC. Trial registration and declaration of registration by authors of randomized controlled trials. *Transplantation* 2011;**92**(10):1094–100.

Moher 1998
Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? . *Lancet* 1998;**352**(9128):609–13.

Monfared 2009
Monfared SSMS, Vahidi H, Abdolghaffari AH, Nikfar S, Abdollahi M. Antioxidant therapy in the management of acute, chronic and post-ERCP pancreatitis: a systematic review. *World Journal of Gastroenterology* 2009;**15**(36): 4481–90.

Owen 2000
Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. *European Journal of Cancer* 2000;**36**(10):1235–47.

Pezzilli 2005
Pezzilli R, Morselli Labate AM, Ceciliato R, Frulloni L, Cavestro GM, Comparato G, et al. Quality of life in patients with chronic pancreatitis. *Digestive Liver Disease* 2005;**37**:181–9.

Ramos-Márquez 2008
Ramos-Márquez ME, Siller-López F. Current antioxidant molecular therapies for oxidative stress-related ailments. *Current Gene Therapy* 2008;**8**(4):256–63.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rose 1986
Rose P, Fraine E, Hunt LP, Acheson DW, Braganza JM. Dietary antioxidants and chronic pancreatitis. *Human Nutrition - Clinical Nutrition* 1986;**40**(2):151–64.

Sala 2002
Sala A, Recio MD, Giner RM, Manez S, Tournier H, Schinella G, et al. Anti-inflammatory and antioxidant properties of *Helichrysum italicum*. *The Journal of Pharmacy and Pharmacology* 2002;**54**(3):365–71.

Schneider 2007
Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *Journal of Gastroenterology* 2007;**42**(2):101–19.

Schulz 1995
Schulz KF, Chalmers I, Hayer R, Altman D. Empirical evidence of bias. *JAMA* 1995;**273**(5):408–12.

Spanier 2008
Spanier BW, Dijkgraaf MG, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. *Best Practice and Research. Clinical Gastroenterology* 2008;**22**:45–63.

Stedman 2011
Stedman MR, Curtin F, Elbourne DR, Kesselheim AS, Brookhart MA. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2011;**40**(6):1732–4.

Temple 2000
Temple NJ. Antioxidants and disease: more questions than answers. *Nutrition Research* 2000;**20**(3):449–59.

van Esch 2006
van Esch AA, Wilder-Smith OH, Jansen JB, van Goor H, Drenth JP. Pharmacological management of pain in chronic pancreatitis. *Digestive Liver Disease* 2006;**38**(7):518–26.

Wehler 2004
Wehler M, Nichterlein R, Fischer B, Farnbacher M, Reulbach U, Hahn EG, et al. Factors associated with health-related quality of life in chronic pancreatitis. *American Journal of Gastroenterology* 2004;**99**:138–46.

Willett 2002
Willett WC. Balancing life-style and genomics research for disease prevention. *Science* 2002;**296**:695–8.

Witt 2007
Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in the pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* 2007;**132**(4): 1557–73.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Banks 1997

Methods	• Type of trial: double-blind, randomised, placebo-controlled, cross-over trial • Duration of intervention: antioxidant or placebo (4 weeks), washout period (2 weeks), cross-over to placebo or antioxidant (4 weeks)
Participants	• 16 participants (aged > 18 years) with CP who experienced continuous or intermittent episodes of pain (> 2 episodes/wk)
Interventions	• Intervention: allopurinol 300 mg/d • Control: identical placebo
Outcomes	• Pain: ○ Pain scores (descriptive pain intensity scale, numerical pain intensity scale and visual analogue scale) ○ McGill Pain Questionnaire • Use of pain medications: recorded by participants on a daily basis • Activities of daily living: weekly activities of daily living questionnaire • Mean uric acid levels: measured at beginning of treatment, at week 2 and at the end of each treatment period • Adverse effects
Notes	Study performed in Boston, United States of America

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by hospital pharmacy
Allocation concealment (selection bias)	Low risk	Randomisation concealed by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. Placebo was identical to intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	6 of 16 (38%) participants withdrew 3 did not come to the clinic before the start of study medication (all in allopurinol group). 2 participants (1 in each group) discontinued because of adverse experiences. 1 participant in the placebo first group withdrew from the study at the end of the washout period

Banks 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	No protocol available. All outcomes mentioned in methods are shown in the results
Other bias	Low risk	No other biases identified

Bhardwaj 2009

Methods	• Type of trial: parallel, double-blind, randomised, placebo-controlled trial • Duration of intervention: 6 months
Participants	• 147 patients with CP (aged > 12 years) presenting with significant pancreatic pain. Pain was considered significant if at least 1 episode of pain every month required analgesics during the preceding 3 months, or at least 1 episode of severe pain required hospitalisation during the preceding 3 months
Interventions	• Intervention: combination antioxidants (daily 600 μg selenium, 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol and 2 g methionine) • Control: identical placebo
Outcomes	• Pain: reduction in number of painful days per month • Use of pain medication: numbers of oral analgesic tablets and parenteral injections per month • Number of attacks of pancreatitis: number of attacks of severe pancreatitis requiring hospitalisation • Man-days lost: number of man-days lost per month • Oxidative stress markers and antioxidant status • Adverse effects
Notes	Study performed in New Delhi, India

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence was computer-generated by independent statistician
Allocation concealment (selection bias)	Low risk	Concealed allocation. Separate individuals generated the allocation sequence, enrolled participants and assigned participants to groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. Placebo was identical to intervention

Bhardwaj 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	In total, 40 (27%) participants (27 in the placebo group and 13 in the intervention group) were lost at some time during the study. Not all reasons for these losses are specified
Selective reporting (reporting bias)	Low risk	The study protocol is available. All outcomes in the protocol were reported. Additionally, the number of man-days lost per month as the result of pain was reported in the article but was not specified in the protocol
Other bias	Low risk	No other biases identified

Bilton 1994a

Methods	• Type of trial: double-blind, randomised, placebo-controlled, cross-over trial (Braganza 2010) • Duration of intervention: antioxidants or placebo (10 weeks), cross-over (no washout period) to placebo or antioxidants (10 weeks)
Participants	• 30 participants with: ○ recurrent acute pancreatitis, at least 2 documented attacks of pancreatitis in the previous year ○ CP, constant pain suggestive of a pancreatic origin, including 'alcoholic' (weekly equivalent of > 60 g per day in women or > 80 g per day in men for at least 1 year before the first attack) and idiopathic cases • Participants with acute pancreatitis and CP were randomly assigned separately
Interventions	• Intervention: 3 daily doses of 800 mg S-adenosylmethionine (SAMe) sulfate-p-toluenesulfonate • Control: placebo
Outcomes	• Pain: ○ Daily pain diary: visual analogue scale ○ Descriptive pain score sheet: incorporating 11 descriptors of pancreatic pain • Attacks of pancreatitis: verified by general practitioners at 10 weeks and at the end of the study • Oxidative stress markers and antioxidant status
Notes	Study performed in Manchester, England

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Bilton 1994a (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Randomisation was concealed by envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study, using placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	10 of 30 (33%) participants withdrew (6 for gastrointestinal intolerance, 3 requiring urgent medical treatment, 1 who defaulted)
Selective reporting (reporting bias)	Low risk	No discrepancies between methods and results
Other bias	Low risk	No other biases identified

Bilton 1994b

Methods	• Type of trial: double-blind, randomised, placebo-controlled, cross-over trial (Braganza 2010) • Duration of intervention: antioxidants or placebo (10 weeks), cross-over (no washout period) to placebo or antioxidants (10 weeks)
Participants	• 14 participants with: ○ recurrent acute pancreatitis, at least 2 documented attacks of pancreatitis in the previous year ○ CP, constant pain suggestive of a pancreatic origin, including 'alcoholic' (weekly equivalent of > 60 g per day in women or > 80 g per day in men for at least 1 year before the first attack) and idiopathic cases • Participants with acute pancreatitis and CP were randomly assigned separately
Interventions	Intervention: combination antioxidants (daily 800 mg S-adenosylmethionine (SAMe) sulfate-p-toluenesulfonate and 600 μg selenium and 9000 IU β-carotene) Control: placebo
Outcomes	• Pain: ○ Daily pain diary: visual analogue scale ○ Descriptive pain score sheet: incorporating 11 descriptors of pancreatic pain • Attacks of pancreatitis: verified by general practitioners at 10 weeks and at the end of the study • Oxidative stress markers and antioxidant status
Notes	Original goal was to include 30 participants. Study was terminated early because of adverse events Study performed in Manchester, England

Bilton 1994b (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Randomisation was concealed by envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded study, using placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	6 (43%) of 14 patients withdrew (3 for gastrointestinal adverse effects, 2 with unrelated medical problems, 1 who defaulted)
Selective reporting (reporting bias)	Low risk	No discrepancies between methods and results
Other bias	High risk	Study was terminated early as the result of unexpected adverse events. No formal stopping rule was applied, and study authors did not state that analysis was corrected for early termination

Deprez 2003

Methods	• Type of trial: open, randomised, controlled, cross-over trial • Duration of intervention: dietary counselling with antioxidants vs dietary counselling alone (3 months), cross-over (no washout period) to dietary counselling alone or antioxidants with dietary counselling (3 months)
Participants	• 30 participants (aged 18 to 60 years) with CP (not further specified). Average pain VAS was 31.7%
Interventions	• Intervention: dietary counselling plus antioxidant supplementation (3 times daily Quatral, containing 25 mg vitamin E, 120 mg vitamin C, 6 mg β-carotene (1 mg vitamin A), 100 μg selenium, 15 mg zinc) • Control: dietary counselling aiming to correct all errors detected during a preliminary dietary evaluation
Outcomes	• Diatary assessment • Pain: pain visual analogue scale (VAS) and number of participants with pain • Oxidative stress markers and antioxidant levels • Nutritional and metabolic assessment (BMI, fat mass, basal metabolism) • Exocrine and endocrine pancreatic function.

Deprez 2003 (*Continued*)

Notes	• Published only in abstract form • Study performed in Brussels, Belgium

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not performed (open trial)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Published only in abstract form. Pain data not well reported
Other bias	Unclear risk	Published only in abstract form

Durgaprasad 2005

Methods	• Type of trial: parallel, single-blind, randomised, placebo-controlled trial • Duration of intervention: 6 weeks
Participants	• 20 participants (aged 18 to 65 years) with non-alcoholic CP, with abdominal pain not related to other gastrointestinal or systemic disease
Interventions	• Intervention: combination antioxidants (3 times daily 500 mg curcumin and 5 mg piperine) • Control: identical placebo
Outcomes	• Pain: visual analogue scale assessed before and after treatment • Use of pain medication • Oxidative stress markers and antioxidant status • Adverse effects
Notes	Study performed in Manipal, India

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Durgaprasad 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of randomisation is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	5 (25%) participants did not return for evaluation and were not assessed
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methods are shown in results. Data on use of analgesics not shown but use of analgesics is shortly described. No protocol available
Other bias	Unclear risk	Study authors say diabetic patients will be excluded, but in the characteristics of participants section, 6 are described as having diabetes mellitus

Jarosz 2010

Methods	• Type of trial: parallel, open, randomised, controlled trial • Duration of intervention: 6 months
Participants	91 participants (aged 18 to 60 years) with proven (by imaging) alcoholic CP (daily 20 mL for 7 years), with abdominal pain
Interventions	• Intervention: combination antioxidants (vitamin C and vitamin E) • Control: standard treatment (i.e. no alcohol consumption, high-energy frequent diet and painkillers (buskopan, paracetamol) if needed)
Outcomes	• Number of participants becoming pain free • Number of participants with attack of pancreatitis • Disease-related complications (weight loss, exocrine and endocrine pancreatic function) • Oxidative stress markers and antioxidant status
Notes	Study performed in Warsaw, Poland

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated. Stated only that a random code was used

Jarosz 2010 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	24 (26%) of 91 participants were excluded: 10 in the standard treatment group, and 14 in the antioxidant group. Reasons for exclusion: continued alcohol consumption, loss to follow-up and lack of compliance with study medication
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section are reported
Other bias	Low risk	No other biases identified

Kirk 2006

Methods	• Type of trial: double-blind, randomised, placebo-controlled, cross-over trial • Duration of intervention: antioxidants or placebo (10 weeks), cross-over (no washout period) to placebo or antioxidants (10 weeks)
Participants	• 36 participants (aged 16 to 75 years) with non-gallstone CP and chronic abdominal pain. Participants had to meet 1 of the following criteria. ○ Radiological abnormality of the pancreas consistent with CP (e.g. calcification) ○ Pancreatic duct abnormality at ERCP ○ Evidence of exocrine pancreatic insufficiency on para-aminobenzoic acid testing
Interventions	• Intervention: combination antioxidants (4 times daily 75 μg selenium, 3 mg β-carotene, 47 mg d-α-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C) and 400 mg methionine) • Control: identical placebo
Outcomes	• Pain: diaries incorporating visual analogue scales assessing pain intensity, pain relief and mood on a daily basis • Quality of life: Short Form-36 questionnaire • Oxidative stress markers and antioxidant status • Adverse effects
Notes	Study performed in Belfast, Northern Ireland

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Kirk 2006 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not specified
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Identical placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	17 (47%) of 36 participants withdrew or were lost to follow-up. 10 had first placebo and 7 first antioxidants. This was attributed to the length of the study period, poor participant motivation and, in some cases, ongoing problems with alcohol dependence
Selective reporting (reporting bias)	High risk	No protocol available. Pain diaries were excluded from analyses because of inconsistent completion
Other bias	Low risk	Fat-soluble vitamins such as vitamin E tended to remain slightly elevated at the end of the study, but results of this study and of previous studies provide evidence against a significant bias due to carry-over effect

Nandi 2002

Methods	• Type of trial: parallel, randomised, placebo-controlled trial • Duration of intervention: 6 months
Participants	• 25 patients with CP. No information regarding preintervention pain levels
Interventions	• Intervention: combination antioxidants (daily 600 μg selenium, 0.54 g ascorbic acid (vitamin C), 9000 IU β-carotene, 270 IU α-tocopherol (vitamin E) and 2 g methionine) • Control: placebo (unclear whether identical)
Outcomes	• Pain: pain score (own scale, with maximal 12 points) and reduction in number of painful days per month • Oxidative stress markers and antioxidant status
Notes	• Published only in abstract form • Study performed in New Delhi, India

Risk of bias	***Risk of bias***

Nandi 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Published only as an abstract
Other bias	Unclear risk	Published only as an abstract

Salim 1991

Methods	• Type of trial: parallel, 3-armed, double-blind, randomised, placebo-controlled trial • Duration of intervention: until 24 hours pain free (mean = 45 hours)
Participants	• 78 participants presenting at the hospital with a recurrent episode of abdominal pain caused by alcohol-induced CP meeting the following criteria. ○ Patient presented within 2 hours of onset of epigastric pain radiating to the back ○ No treatment had been given for the pain ○ Patient had not abstained from alcohol ○ No generalised peritonitis was clinically detectable
Interventions	• Intervention arm 1: 4 times daily 50 mg allopurinol • Intervention arm 2: 4 times daily 500 mg dimethylsulfoxide • Control: 4 times daily placebo
Outcomes	Participants were questioned 3 times each day and were physically examined twice daily • Pain: percentage of participants becoming pain free 12, 24, 36 and 48 hours after start of the intervention • Percentage of participants with epigastric tenderness (daily) • Percentage of participants tolerating free fluids for 12 hours (36, 48 and 72 hours after start of treatment) • Percentage of participants tolerating 3 solid meals (daily) • Percentage of participants discharged home (daily) • Serum: white blood cell count, amylase and lactate dehydrogenase • Adverse effects
Notes	Study performed in Baghdad, Iraq

Salim 1991 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not stated
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. Placebo was given in same amount (iv) and on same schedule
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four of 27 participants in the placebo group, three of 25 in the allopurinol group and five of 26 in the dimethylsulfoxide group were not assessed. Reasons were given. Both per-protocol and intention-to-treat analyses were performed
Selective reporting (reporting bias)	Unclear risk	No protocol available. No clear specification of outcomes in the methods section
Other bias	Low risk	No other biases

Siriwardena 2012

Methods	• Type of trial: parallel, double-blind, randomised, placebo-controlled trial • Duration of intervention: 6 months
Participants	70 patients with painful chronic pancreatitis (proven by imaging) with a baseline daily pain score of 5 or greater for at least 7 days during a prerandomisation run-in period of 1 month
Interventions	• Intervention: combination antioxidants (38.5 mg selenium yeast, of which 50 g l-selenomethionine, 113.4 mg d-tocopherol acetate, 126.3 mg ascorbic acid and 480 mg l-methionine) • Control: identical placebo
Outcomes	• Pain score: visual analogue score, change in pain score from baseline • Pain diaries: daily pain scores (analysed as average of daily scores over study period) • Brief Pain Inventory scores • Quality of life questionnaires: EORTC-QLQC, QLQ-PAN28, EuroQOL, EQ-5D and EQ visual analogue scale • Oxidative stress markers and antioxidant status • Use of opioid analgesics • Hospital admissions for attacks of pancreatitis or complications • Adverse effects

Siriwardena 2012 (*Continued*)

Notes	Study performed in Manchester, United Kingdom

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Concealed by central allocation (by pharmacy)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	22 (23%) of 92 participants withdrew or were lost to follow-up. Withdrawals were similar, by treatment allocation and in age, sex and baseline pain scores
Selective reporting (reporting bias)	Low risk	According to the registration form, the study authors intended to also present 'Time in pain' and 'Economic evaluation' as part of their secondary outcomes. These outcomes are not reported in the published paper. However, these are secondary outcomes that are not likely to significantly affect the results of the trial
Other bias	Low risk	No other biases identified

Uden 1990

Methods	• Type of trial: double-blind, randomised, placebo-controlled, cross-over trial • Duration of intervention: antioxidants or placebo (10 weeks), cross-over (no washout period) to placebo or antioxidants (10 weeks)
Participants	• 23 patients with: ○ recurrent acute pancreatitis, at least 2 documented attacks of pancreatitis in the previous year, when ERCP and a test of exocrine pancreatic function were unequivocally normal 6 to 8 weeks after recovery, or ○ CP, constant pain suggestive of a pancreatic origin, including 'alcoholic' (weekly equivalent of > 60 g per day in women or > 80 g per day in men for at least 1 year before the first attack) and idiopathic cases

Uden 1990 (*Continued*)

Interventions	• Intervention: combination antioxidants (daily 600 μg selenium, 9000 IU β-carotene, 0.54 g vitamin C, 270 IU vitamin E, 2 g methionine) • Control: identical placebo
Outcomes	• Pain: • ○ Diaries incorporating a visual analogue scale completed on a daily basis ○ Pain Vocabulary Scoresheet (at start, cross-over and end of study) • Frequency of attacks of pancreatitis • Psychological aspects: McGill Standard Pain Questionnaire, Zung Questionnaire, pain experience questionnaire and pain locus of control • Oxidative stress markers and antioxidant status • Adverse effects
Notes	Study performed in Manchester, England

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Double-blind, double-dummy, coordinated by a senior pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Identical placebos, except for subtle differences (i.e. the selenium-placebo had a distinctive sweet taste, and the methionine-placebo lacked the garlic-like odour of the true substance)
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 (14%) participants lost to follow-up: 1 required surgery early in the trial, 1 got pregnant, 1 changed jobs and 1 was accidentally changed from placebo to antioxidant group 1 (4%) participant's data were not analysed because during the trial, after biochemical analysis, it turned out that the participant had high baseline levels of vitamin E (participant was taking vitamin E-containing supplement before the trial)
Selective reporting (reporting bias)	Low risk	All outcomes in the methods section are reported
Other bias	Low risk	No other biases identified

Abbreviations:
BMI: body mass index.
CP: chronic pancreatitis.
EORTC-QLQC: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.
EQ-5D: EuroQOL 5-Dimension Questionnaire.
ERCP: endoscopic retrograde cholangiopancreatography.
EuroQOL: European Quality of Life Group.
QLQ-PAN28: Quality of Life Questionnaire-Pancreatic modification.
SAMe: S-adenosylmethionine.
VAS: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bagul 2006	Not a randomised study
Bhardwaj 2004	Not a randomised study
Bhardwaj 2006	Not a randomised study
Braganza 1991	Book chapter. Review of topic
De las Heras 2000	Not a randomised study
Klapdor 2012	Not a randomised study. The intervention (vitamin D) is not a known antioxidant agent
Martinez-Torres 2009	Randomised controlled trial on acute pancreatitis
Matthew 1996	Not a randomised study (cross-sectional)
Milnerowicz 2005	Not a randomised study
Mosler 2005	Randomised controlled trial on acute pancreatitis
Nakamura 1996	Not a randomised study. Study focused on effect of pancreatic insufficiency
Romagnuolo 2008	Randomised controlled trial on acute pancreatitis
Shah 2010	Not a randomised study
Shalimar 2011	Not a randomised study
Sinwardena 2006	Randomised controlled trial on acute pancreatitis
Uden 1988	Not a randomised study (case-control study)

Characteristics of ongoing studies *[ordered by study ID]*

EUROPAC-2

Trial name or title	Pain Treatment of Hereditary and Idiopathic Pancreatitis
Methods	3-armed, double-blind, placebo-controlled, randomised, parallel-group study
Participants	Patients with hereditary pancreatitis or idiopathic chronic pancreatitis
Interventions	Group 1: daily doses of 300 µg organic selenium, 18 mg β-carotene, 750 mg vitamin C, 240 mg vitamin E, 2700 mg methionine Group 2: magnesium-L-aspartate-hydrochloride 365 mg/d Group 3: placebo
Outcomes	Primary outcome measures: • Reduction in number of days of pancreatic pain during 12 continuous months of treatment Secondary outcome measures: • Disruption of activities of normal living • Analgesic use for pancreatic pain • Number of days of hospitalisation for conditions related to pancreatitis • Quality of life (QoL) measures • Markers of inflammatory response and activity of the pancreas • Changes in urinary levels of magnesium, selenium and vitamin C over the duration of the study • Antioxidant response as measured by urinary thiobarbituric acid levels • Response in participants with hereditary pancreatitis and idiopathic chronic pancreatitis • Correlationg of response with gene mutations underlying hereditary pancreatitis (PRSS1, other) and idiopathic chronic pancreatitis (SPINK1, CFTR, other) • Data acquisition, including markers of inflammatory response during acute attack of chronic pancreatitis
Starting date	June 2004
Contact information	Markus M Lerch, Professor of Medicine; 03834-86 ext 7230. lerch@uni-greifswald.de Julia V Mayerle, MD; 03834-86 ext 7244. mayerle@uni-greifswald.de
Notes	Contact: Julia V Mayerle, MD

DATA AND ANALYSES

Comparison 1. Antioxidant versus control intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain visual analogue scale score-cross-over trials	2	44	Mean Difference (Fixed, 95% CI)	-0.34 [-0.67, -0.01]
2 Pain visual analogue scale score-parallel trials	2	85	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-1.07, 0.56]
3 Pain visual analogue scale score-combined all trials	4		Mean Difference (Fixed, 95% CI)	-0.33 [-0.64, -0.02]
4 Pain-free participants-parallel trials	3	264	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.95, 3.15]
5 Adverse effects	8	404	Risk Ratio (M-H, Fixed, 95% CI)	4.93 [2.21, 11.03]
5.1 Cross-over trials	5	192	Risk Ratio (M-H, Fixed, 95% CI)	5.8 [1.56, 21.53]
5.2 Parallel trials	3	212	Risk Ratio (M-H, Fixed, 95% CI)	4.43 [1.60, 12.29]
6 Adverse effects-sensitivity analysis of parallel and cross-over trials	8	404	Risk Ratio (M-H, Fixed, 95% CI)	4.93 [2.21, 11.03]
7 Adverse effects-sensitivity analysis with risk difference	8	404	Risk Difference (M-H, Fixed, 95% CI)	0.13 [0.08, 0.19]
8 Number of pancreatitis attacks-cross-over trials, unpaired analysis	3	108	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.10, 4.10]
9 Vitamin C levels (mg/dL)-parallel trials	3	237	Std. Mean Difference (IV, Random, 95% CI)	1.46 [1.00, 1.91]
10 Vitamin C levels (mg/dL)-sensitivity analysis of parallel and cross-over trials	6	343	Std. Mean Difference (IV, Random, 95% CI)	1.01 [0.48, 1.53]
11 Vitamin E levels (mg/dL)-parallel trials	3	237	Std. Mean Difference (IV, Random, 95% CI)	1.32 [0.51, 2.13]
12 Vitamin E levels (mg/dL)-sensitivity analysis of parallel and cross-over trials	7	381	Std. Mean Difference (IV, Random, 95% CI)	1.12 [0.47, 1.78]
13 Selenium levels (μg/dL)-sensitivity analysis of parallel and cross-over trials	5	214	Mean Difference (IV, Random, 95% CI)	14.55 [4.38, 24.71]
14 β-Carotene levels (μg/dL)-sensitivity analysis of parallel and cross-over trials	5	214	Std. Mean Difference (IV, Random, 95% CI)	1.46 [0.44, 2.48]

Analysis 1.1. Comparison 1 Antioxidant versus control intervention, Outcome 1 Pain visual analogue scale score-cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 1 Pain visual analogue scale score—cross-over trials

Study or subgroup	Antioxidants N	Control N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Banks 1997	8	8	-0.28 (0.25)		45.8 %	-0.28 [-0.77, 0.21]
Uden 1990	14	14	-0.39 (0.23)		54.2 %	-0.39 [-0.84, 0.06]
Total (95% CI)	**22**	**22**			**100.0 %**	**-0.34 [-0.67, -0.01]**

Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 2.01 (P = 0.045)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Antioxidant versus control intervention, Outcome 2 Pain visual analogue scale score-parallel trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

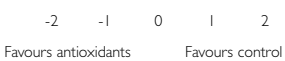
Outcome: 2 Pain visual analogue scale score—parallel trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Durgaprasad 2005	8	5.81 (2.09)	7	6.57 (1.38)		21.2 %	-0.76 [-2.53, 1.01]
Siriwardena 2012	33	2.93 (1.96)	37	3.05 (1.96)		78.8 %	-0.12 [-1.04, 0.80]
Total (95% CI)	**41**		**44**			**100.0 %**	**-0.26 [-1.07, 0.56]**

Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

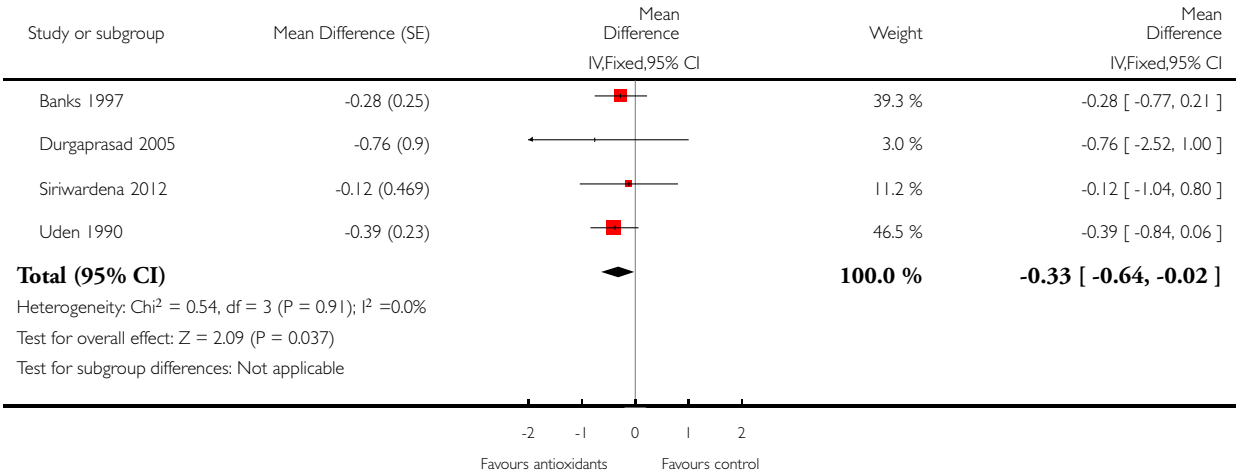


Analysis 1.3. Comparison 1 Antioxidant versus control intervention, Outcome 3 Pain visual analogue scale score-combined all trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 3 Pain visual analogue scale score—combined all trials

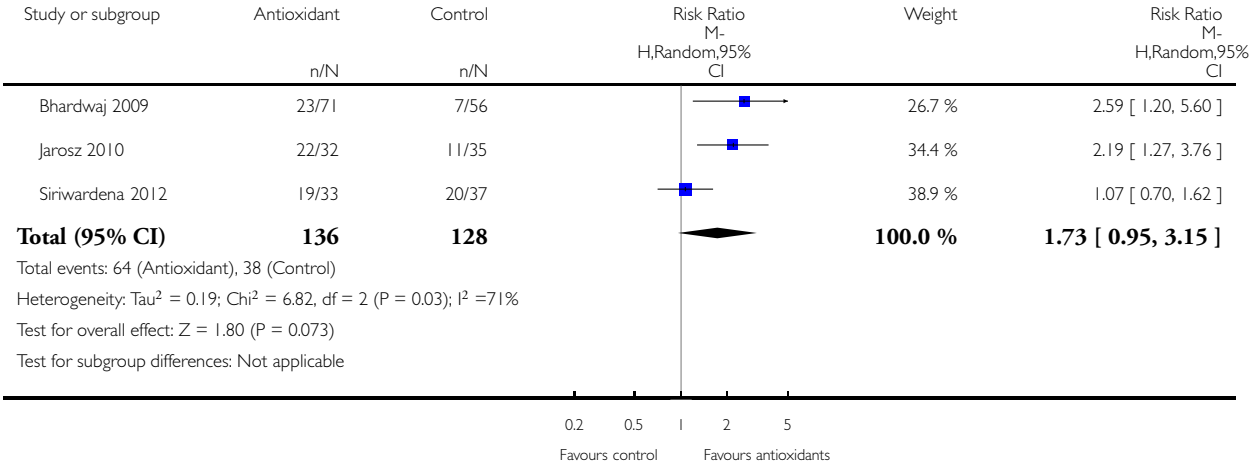


Analysis 1.4. Comparison 1 Antioxidant versus control intervention, Outcome 4 Pain-free participants-parallel trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 4 Pain-free participants—parallel trials

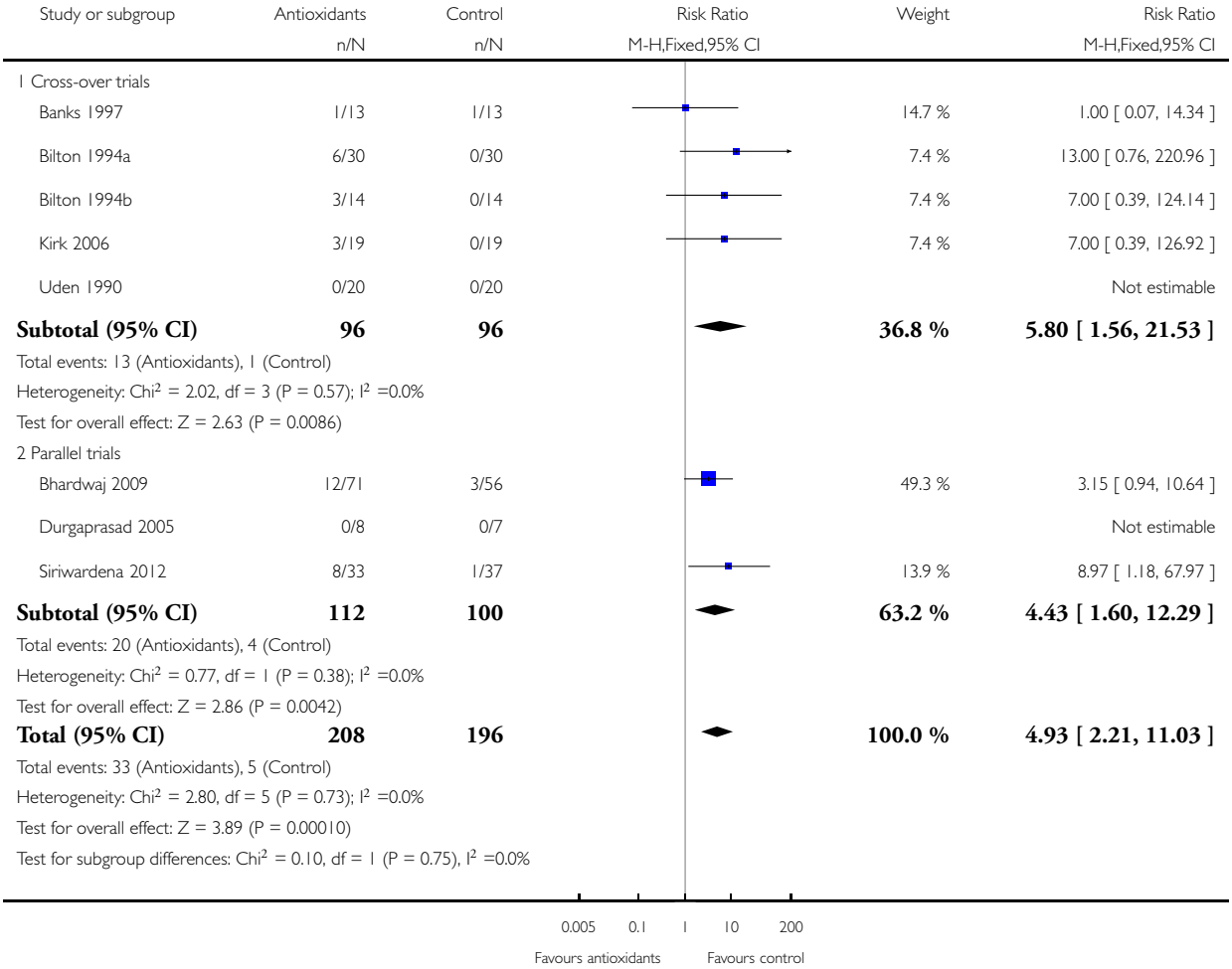


Analysis 1.5. Comparison 1 Antioxidant versus control intervention, Outcome 5 Adverse effects.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 5 Adverse effects



Analysis 1.6. Comparison 1 Antioxidant versus control intervention, Outcome 6 Adverse effects-sensitivity analysis of parallel and cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 6 Adverse effects—sensitivity analysis of parallel and cross-over trials

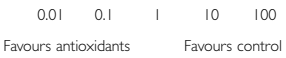
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Banks 1997	1/13	1/13		14.7 %	1.00 [0.07, 14.34]
Bhardwaj 2009	12/71	3/56		49.3 %	3.15 [0.94, 10.64]
Bilton 1994a	6/30	0/30		7.4 %	13.00 [0.76, 220.96]
Bilton 1994b	3/14	0/14		7.4 %	7.00 [0.39, 124.14]
Durgaprasad 2005	0/8	0/7			Not estimable
Kirk 2006	3/19	0/19		7.4 %	7.00 [0.39, 126.92]
Siriwardena 2012	8/33	1/37		13.9 %	8.97 [1.18, 67.97]
Uden 1990	0/20	0/20			Not estimable
Total (95% CI)	**208**	**196**		**100.0 %**	**4.93 [2.21, 11.03]**

Total events: 33 (Antioxidants), 5 (Control)

Heterogeneity: $Chi^2 = 2.80$, df = 5 (P = 0.73); $I^2 = 0.0\%$

Test for overall effect: Z = 3.89 (P = 0.00010)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Antioxidant versus control intervention, Outcome 7 Adverse effects-sensitivity analysis with risk difference.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 7 Adverse effects—sensitivity analysis with risk difference

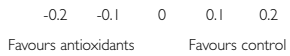
Study or subgroup	Antioxidants n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Banks 1997	1/13	1/13		6.5 %	0.0 [-0.20, 0.20]
Bhardwaj 2009	12/71	3/56		31.2 %	0.12 [0.01, 0.22]
Bilton 1994a	6/30	0/30		14.9 %	0.20 [0.05, 0.35]
Bilton 1994b	3/14	0/14		7.0 %	0.21 [-0.02, 0.45]
Durgaprasad 2005	0/8	0/7		3.7 %	0.0 [-0.22, 0.22]
Kirk 2006	3/19	0/19		9.5 %	0.16 [-0.02, 0.34]
Siriwardena 2012	8/33	1/37		17.4 %	0.22 [0.06, 0.37]
Uden 1990	0/20	0/20		10.0 %	0.0 [-0.09, 0.09]
Total (95% CI)	**208**	**196**		**100.0 %**	**0.13 [0.08, 0.19]**

Total events: 33 (Antioxidants), 5 (Control)

Heterogeneity: Chi^2 = 13.46, df = 7 (P = 0.06); I^2 =48%

Test for overall effect: Z = 4.53 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Antioxidant versus control intervention, Outcome 8 Number of pancreatitis attacks-cross-over trials, unpaired analysis.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 8 Number of pancreatitis attacks—cross-over trials, unpaired analysis

Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bilton 1994a	2/20	3/20		40.8 %	0.67 [0.12, 3.57]
Bilton 1994b	3/14	1/14		33.8 %	3.00 [0.35, 25.46]
Uden 1990	0/20	6/20		25.5 %	0.08 [0.00, 1.28]
Total (95% CI)	**54**	**54**		**100.0 %**	**0.64 [0.10, 4.10]**

Total events: 5 (Antioxidants), 10 (Control)

Heterogeneity: $Tau^2 = 1.47$; $Chi^2 = 4.43$, df = 2 (P = 0.11); $I^2 = 55\%$

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Antioxidant versus control intervention, Outcome 9 Vitamin C levels (mg/dL)-parallel trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 9 Vitamin C levels (mg/dL)—parallel trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bhardwaj 2009	62	2.08 (0.82)	38	1.19 (0.54)		37.6 %	1.21 [0.78, 1.65]
Jarosz 2010	32	0.44 (0.21)	35	0.14 (0.05)		29.2 %	1.98 [1.39, 2.58]
Siriwardena 2012	33	8.34 (8.76)	37	-0.7 (5.15)		33.1 %	1.26 [0.75, 1.78]
Total (95% CI)	**127**		**110**			**100.0 %**	**1.46 [1.00, 1.91]**

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 4.69$, df = 2 (P = 0.10); $I^2 = 57\%$

Test for overall effect: Z = 6.30 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Antioxidant versus control intervention, Outcome 10 Vitamin C levels (mg/dL)-sensitivity analysis of parallel and cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 10 Vitamin C levels (mg/dL)—sensitivity analysis of parallel and cross-over trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bhardwaj 2009	62	2.08 (0.82)	38	1.19 (0.54)		18.6 %	1.21 [0.78, 1.65]
Bilton 1994a	20	0.91 (0.39)	20	0.74 (0.38)		16.3 %	0.43 [-0.20, 1.06]
Bilton 1994b	14	0.69 (0.35)	14	0.76 (0.71)		15.0 %	-0.12 [-0.86, 0.62]
Jarosz 2010	32	0.44 (0.21)	35	0.14 (0.05)		16.8 %	1.98 [1.39, 2.58]
Kirk 2006	19	0.45 (0.13)	19	0.32 (0.1)		15.6 %	1.10 [0.41, 1.78]
Siriwardena 2012	33	8.34 (8.76)	37	-0.7 (5.15)		17.7 %	1.26 [0.75, 1.78]
Total (95% CI)	**180**		**163**			**100.0 %**	**1.01 [0.48, 1.53]**

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 23.98$, df = 5 (P = 0.00022); $I^2 = 79\%$

Test for overall effect: Z = 3.77 (P = 0.00016)

Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Antioxidant versus control intervention, Outcome 11 Vitamin E levels (mg/dL)-parallel trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 11 Vitamin E levels (mg/dL)—parallel trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bhardwaj 2009	62	1.44 (0.65)	38	0.81 (0.24)		34.6 %	1.17 [0.74, 1.61]
Jarosz 2010	32	0.47 (0.16)	35	0.21 (0.05)		31.5 %	2.21 [1.60, 2.83]
Siriwardena 2012	33	7.42 (17.95)	37	-1.88 (10.02)		33.9 %	0.64 [0.16, 1.12]
Total (95% CI)	**127**		**110**			**100.0 %**	**1.32 [0.51, 2.13]**

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 15.51$, df = 2 (P = 0.00043); $I^2 = 87\%$

Test for overall effect: Z = 3.18 (P = 0.0015)

Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Antioxidant versus control intervention, Outcome 12 Vitamin E levels (mg/dL)-sensitivity analysis of parallel and cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

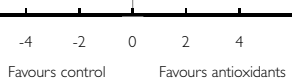
Outcome: 12 Vitamin E levels (mg/dL)—sensitivity analysis of parallel and cross-over trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Bhardwaj 2009	62	1.44 (0.65)	38	0.81 (0.24)		15.5 %	1.17 [0.74, 1.61]
Bilton 1994a	20	0.91 (0.39)	20	1 (0.42)		14.5 %	-0.22 [-0.84, 0.40]
Bilton 1994b	14	1.1 (0.31)	14	1 (0.27)		13.7 %	0.33 [-0.41, 1.08]
Jarosz 2010	32	0.47 (0.16)	35	0.21 (0.05)		14.5 %	2.21 [1.60, 2.83]
Kirk 2006	19	1.75 (0.23)	19	1.29 (0.09)		12.8 %	2.58 [1.70, 3.46]
Siriwardena 2012	33	7.42 (17.95)	37	-1.88 (10.02)		15.2 %	0.64 [0.16, 1.12]
Uden 1990	19	2 (0.77)	19	1.1 (0.57)		13.9 %	1.30 [0.59, 2.01]
Total (95% CI)	**199**		**182**			**100.0 %**	**1.12 [0.47, 1.78]**

Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 48.20$, df = 6 ($P<0.00001$); $I^2 = 88\%$

Test for overall effect: $Z = 3.37$ ($P = 0.00076$)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Antioxidant versus control intervention, Outcome 13 Selenium levels (μg/dL)-sensitivity analysis of parallel and cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

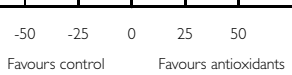
Outcome: 13 Selenium levels (μ g/dL)—sensitivity analysis of parallel and cross-over trials

Study or subgroup	Antioxidants N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bilton 1994a	20	8.4 (6)	20	8.5 (7.4)		21.5 %	-0.10 [-4.28, 4.08]
Bilton 1994b	14	11.2 (8.5)	14	5.6 (4.8)		21.1 %	5.60 [0.49, 10.71]
Kirk 2006	19	28.5 (7.5)	19	12.4 (2.7)		21.7 %	16.10 [12.52, 19.68]
Siriwardena 2012	33	42.73 (32.27)	37	0.92 (12.39)		17.2 %	41.81 [30.10, 53.52]
Uden 1990	19	18.8 (21.8)	19	4.2 (4.5)		18.4 %	14.60 [4.59, 24.61]
Total (95% CI)	**105**		**109**			**100.0 %**	**14.55 [4.38, 24.71]**

Heterogeneity: Tau^2 = 120.36; Chi^2 = 65.60, df = 4 (P<0.00001); I^2 =94%

Test for overall effect: Z = 2.81 (P = 0.0050)

Test for subgroup differences: Not applicable

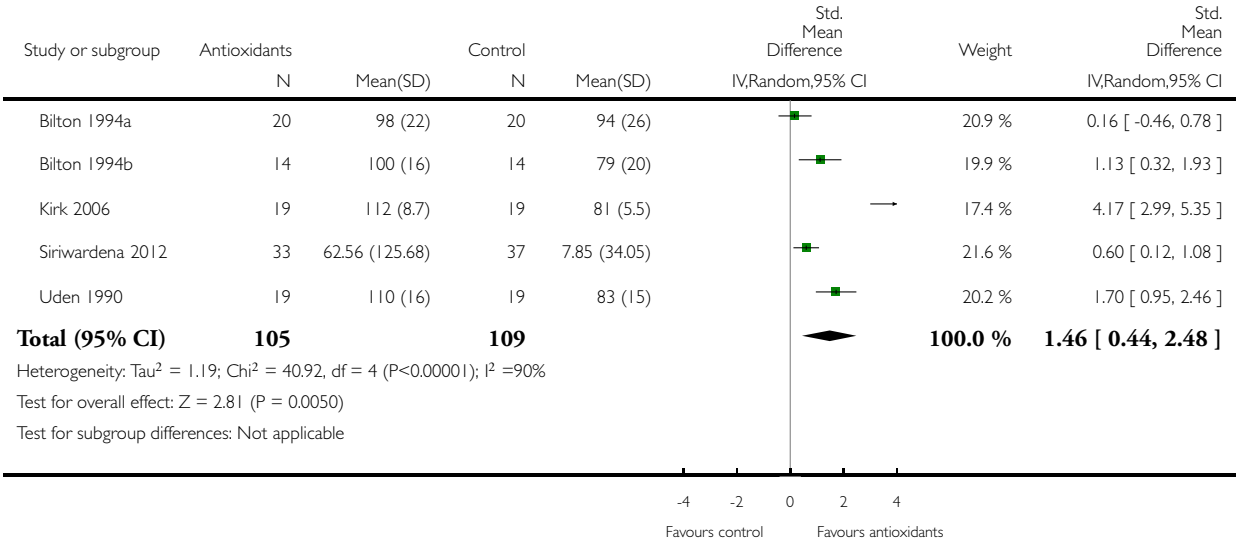


Analysis 1.14. Comparison 1 Antioxidant versus control intervention, Outcome 14 β-Carotene levels (μg/dL)-sensitivity analysis of parallel and cross-over trials.

Review: Antioxidants for pain in chronic pancreatitis

Comparison: 1 Antioxidant versus control intervention

Outcome: 14 β -Carotene levels (μ g/dL)—sensitivity analysis of parallel and cross-over trials



ADDITIONAL TABLES

Table 1. Pain outcome measures

Study/Pain outcome measure	VAS pain score	Proportion of pain-free participants	Numerical pain scale	Categorical pain scale	Descriptive pain score	Number of painful days	McGill Pain Questionnaire	SF-36 pain component
Banks 1997	X	-	X	X	-	-	X	-
Bhardwaj 2009	-	X	-	-	-	X	-	-
Bilton 1994a	X	-	-	-	X	-	-	-
Bilton 1994b	X	-	-	-	X	-	-	-

Table 1. Pain outcome measures (*Continued*)

Deprez 2003	X	X	-	-	-	-	-	-
Durgaprasad 2005	X	-	-	-	-	-	-	-
Jarosz 2010	-	X	-	-	-	-	-	-
Kirk 2006	X	-	-	-	-	-	-	X
Nandi 2002	-	-	X	-	-	X	-	-
Salim 1991	-	-	-	-	-	-	-	-
Siriwardena 2012	X	X	-	-	X	-	-	-
Uden 1990	X	-	-	-	X	-	X	-

Table 2. Baseline characteristics of included trials

Study	Type of trial	No. randomly assigned (IG vs PG)	No. analysed (IG vs PG)	Age (years) (mean (SD))	Gender (male, n (%))	Disease	Disease duration (years) (mean (SD))	Alcohol etiology (n (%))	Alcohol intake (g/d) (mean (SD))	Smokers (n (%))	Initial pain levels
Banks 1997	C	16	13	42 (31-51)[1]	8 (62)	All participants with CP	NA	NA	NA	NA	Continous pain, or > 2 pain episodes per week
Bhardwaj 2009	P	147 (76 vs 71)	127 (71 vs 56)	31.3 (11.4) vs 29.6 (9.3)	24 (34) vs 17 (30)	All participants with CP	4.5 (4.2) vs 4.8 (5.4)	15 (27) vs 25 (35)	103 (82) vs 104 (71)	22 (31) vs 14 (25)	Number of painful days: 9.1 (SD 7.6) vs 7.2 (SD 5.3)
Bilton 1994a	C	30	20	45 (14)	11 (55)	CP and ARP	7.2 (4.1)	2 (10)	NA	8 (40)	NA

Table 2. Baseline characteristics of included trials (*Continued*)

Bilton 1994b	C	14	8	NA	NA	NA	NA	NA	NA	NA	NA
Deprez 2003	C	30	NA	NA	NA	All participants with CP	NA	NA	NA	NA	Overall mean VAS: 31.7%
Durgaprasad 2005	P	20 (10 vs 10)	15 (8 vs 7)	24 (13) vs 28 (17)	7 (88) vs 7 (100)	Non-alcoholic CP	1 to 3	0 (0)	NA	NA	VAS: 5.5 (SD 0.56) vs 5.9 (SD 0.50)
Jarosz 2010	P	91 (46 vs 45)	67 (32 vs 35)	49 (27-58) vs 46 (22-60)[2]	26 (81) vs 27 (77)	Alcoholic CP	NA	91 (100)	NA	NA	NA
Kirk 2006	C	36	19	NA	13 (68)	Non-gallstone CP	NA	NA	NA	NA	NA
Nandi 2002	P	25	NA	NA	NA	All participants with CP	NA	NA	NA	NA	NA
Salim 1991***	P	78 (25 vs 26 vs 27)	66 (22 vs 21 vs 23)	41 (32-61) vs 42 (31-62) vs 39 (31 vs. 65)[3]	21 (95) vs 21 (100) vs 22 (96)	Acute attack of alcoholic CP	8.2 vs 7.7 vs 7.3	78 (100)	NA	NA	Mean number of attacks in previous 3 years: 6.7 vs 5.9 vs 6.1
Siriwardena 2012	P	92 (NA)	70 (33 vs 37)	50 (13) vs 50 (9)	23 (70) vs 27 (73)	All participants with CP	4.2 (2.4) vs 4.9 (4.3)	IG: 24 (73) PG: 27 (73)	IG: 222 (123) PG: 247 (202)	IG: 28 (85) PG: 28 (76)	IG: 3.6 PG: 3.9
Uden 1990	C	23	20	NA	NA	Non-gallstone CP	NA	7 (35)	NA	NA	NA

All data presented as all participants (antioxidant group vs control group), unless otherwise specified.
Abbreviations:
ARP: acute recurrent pancreatitis.
CP: chronic pancreatitis.
C: cross-over.
IG: intervention group.

NA: not available.
P: parallel.

PG: placebo group.
SD: standard deviation.
VAS: visual analogue scale.
[1]Median (range).
[2]Mean (range).
[3]This is a 3-arm trial. Data are presented in the following order: allopurinol vs dimethylsulfoxide vs control.

Table 3. Effects of antioxidants on chronic pain in chronic pancreatitis

Study	Outcome measure(s)	Results (antioxidants vs control)	
Banks 1997	• VAS score (0-100): difference in mean decrease from baseline • McGill score (0-45): difference in mean decrease	• 2.8, P value 0.24 • -0.3, P value 0.75	
Bhardwaj 2009	• Pain-free days/mo: decrease from baseline • Pain-free days/mo: after intervention • Pain-free participants	• 7.37 (6.75) vs 3.21 (3.99), P value < 0.001 • 1.68 (2.80) vs 3.36 (4.35), P value 0.012 • 23/71 (32%) vs 7/56 (13%), P value 0.009	
Bilton 1994a	VAS, descriptive pain score	No differences (no data shown)	
Bilton 1994b	VAS, descriptive pain score	No differences (no data shown)	
Deprez 2003	• Pain VAS score • Number of participants with pain	• Not reported • Only 1 participant with pain at end of study	
Durgaprasad 2005	VAS score (after intervention) (mean (SE))	5.81 (0.74) vs 6.57 (0.74), NS	
Jarosz 2010	• Pain-free participants	• 22/32 (68%) vs 11/56 (31%) , P value 0.002	
Kirk 2006	• Daily VAS • SF-36: pain component (change from baseline)	• Not analysed because of poor reporting by participants • +17 points vs -7 points, P value < 0.05	
Nandi 2002	• Pain score (12 points) • Pain-free days/mo	• 1.25 vs 3.62, NS • 3.75 vs 4.12, NS	

Table 3. Effects of antioxidants on chronic pain in chronic pancreatitis (*Continued*)

Siriwardena 2012	• Change in VAS • Average daily VAS • Pain-free participants	• -2.33 (SD 2.09) vs -1.97 (SD 2.46), P value 0.509 • 2.93 (SD 1.96) vs 3.05 (SD 1.96), P value 0.808 • 19 (58%) vs 20 (54%), NS	
Uden 1990	• VAS • McGill score • Descriptive pain score	• 1.01 (Range 0.16 to 4.26) vs 1.88 (Range 0.22 to 5.76), P value 0.10 • No significant differences • No clear differences	

Abbreviations:
NS: not significant.
VAS: visual analogue scale.

APPENDICES

Appendix 1. CENTRAL search strategy

EBM reviews-Cochrane Central Register of Controlled Trials, 2010, 1st Quarter

1. exp Pancreatitis, Chronic/
2. exp Pancreatitis, Alcoholic/
3. (pancrea$ adj2 chronic$).mp.
4. (Alcohol$ adj2 pancrea$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. (pancrea$ adj2 recurren$).mp.
6. or/1-5
7. exp Free Radicals/ag, ai, ip [Agonists, Antagonists & Inhibitors, Isolation & Purification]
8. exp Antioxidants/
9. exp ascorbic acid/ or exp bilirubin/ or exp butylated hydroxyanisole/ or exp butylated hydroxytoluene/ or exp canthaxanthin/ or exp carotenoids/ or exp catalase/ or exp ergothioneine/ or exp grape seed extract/ or exp melatonin/ or exp nordihydroguaiaretic acid/ or exp probucol/ or exp propyl gallate/ or exp pyrogallol/ or exp quercetin/ or exp selenium/ or exp silymarin/ or exp thioctic acid/ or exp tocopherols/ or exp tocotrienols/ or exp uric acid/ or exp vitamin e/ or exp alpha-tocopherol/ or exp beta-tocopherol/ or exp gamma-tocopherol/ or exp zeta carotene/ or exp beta-carotene/ or exp curcumin/ or exp methionine/ or exp allopurinol/
10. exp Oxidants/
11. exp Oxidation-Reduction/
12. *Reactive Oxygen Species/ai [Antagonists & Inhibitors]
13. exp Free Radical Scavengers/
14. exp Peroxides/ai [Antagonists & Inhibitors]
15. antioxidant$.mp.
16. or/7-15
17. 6 and 16

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) 1950 to March Week 4 2010

1. exp Pancreatitis, Chronic/
2. exp Pancreatitis, Alcoholic/
3. (pancrea$ adj2 chronic$).mp.
4. (Alcohol$ adj2 pancrea$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. (pancrea$ adj2 recurren$).mp.
6. or/1-5
7. exp Free Radicals/ag, ai, ip [Agonists, Antagonists & Inhibitors, Isolation & Purification]
8. exp Antioxidants/
9. exp ascorbic acid/ or exp bilirubin/ or exp butylated hydroxyanisole/ or exp butylated hydroxytoluene/ or exp canthaxanthin/ or exp carotenoids/ or exp catalase/ or exp ergothioneine/ or exp grape seed extract/ or exp melatonin/ or exp nordihydroguaiaretic acid/ or exp probucol/ or exp propyl gallate/ or exp pyrogallol/ or exp quercetin/ or exp selenium/ or exp silymarin/ or exp thioctic acid/ or exp tocopherols/ or exp tocotrienols/ or exp uric acid/ or exp vitamin e/ or exp alpha-tocopherol/ or exp beta-tocopherol/ or exp gamma-tocopherol/ or exp zeta carotene/ or exp beta-carotene/ or exp curcumin/ or exp methionine/ or exp allopurinol/
10. exp Oxidants/
11. exp Oxidation-Reduction/
12. *Reactive Oxygen Species/ai [Antagonists & Inhibitors]
13. exp Free Radical Scavengers/
14. exp Peroxides/ai [Antagonists & Inhibitors]
15. antioxidant$.mp.
16. or/7-15
17. 6 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. drug therapy.fs.
23. randomly.ab.
24. trial.ab.
25. groups.ab.
26. or/18-25
27. exp animals/ not humans.sh.
28. 26 not 27
29. 17 and 28

Appendix 3. EMBASE search strategy

EMBASE 1980 to 2010 Week 12

1. exp alcoholic pancreatitis/
2. exp chronic pancreatitis/
3. (pancrea$ adj2 chronic$).mp.
4. (Alcohol$ adj2 pancrea$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. (pancrea$ adj2 recurren$).mp.
6. or/1-5
7. exp antioxidant/
8. exp ascorbic acid/ or exp bilirubin/ or exp butylated hydroxyanisole/ or exp butylated hydroxytoluene/ or exp canthaxanthin/ or exp carotenoids/ or exp catalase/ or exp ergothioneine/ or exp grape seed extract/ or exp melatonin/ or exp nordihydroguaiaretic acid/ or exp probucol/ or exp propyl gallate/ or exp pyrogallol/ or exp quercetin/ or exp selenium/ or exp silymarin/ or exp thioctic acid/ or exp tocopherols/ or exp tocotrienols/ or exp uric acid/ or exp vitamin e/ or exp alpha-tocopherol/ or exp beta-tocopherol/ or exp gamma-tocopherol/ or exp zeta carotene/ or exp beta-carotene/ or exp curcumin/ or exp methionine/ or exp allopurinol/
9. exp oxidizing agent/

10. exp oxidation reduction reaction/
11. exp antioxidant activity/
12. exp oxidation reduction state/
13. exp Free Radical Scavengers/
14. peroxide/cb, it, dt, pr, pk, pd [Drug Combination, Drug Interaction, Drug Therapy, Pharmaceutics, Pharmacokinetics, Pharmacology]
15. antioxidant$.mp.
16. or/7-15
17. 6 and 16
18. Clinical trial/
19. Randomized controlled trial/
20. Randomization/
21. Single-Blind Method/
22. Double-Blind Method/
23. Cross-Over Studies/
24. Random Allocation/
25. Placebo/
26. Randomi?ed controlled trial$.tw.
27. Rct.tw.
28. Random allocation.tw.
29. Randomly allocated.tw.
30. Allocated randomly.tw.
31. (allocated adj2 random).tw.
32. Single blind$.tw.
33. Double blind$.tw.
34. ((treble or triple) adj blind$).tw.
35. Placebo$.tw.
36. Prospective study/
37. or/18-36
38. Case study/
39. Case report.tw.
40. Abstract report/ or letter/
41. or/38-40
42. 37 not 41
43. 17 and 42

Appendix 4. CPCI-S search strategy

Conference Proceedings Citation Index-Science (CPCI-S)-1990 to present
13. #12 AND #11
12. Topic=(pancreatitis)
11. #10 OR #8 OR #6 OR #3 OR #2 OR #1
10. #9 AND #4
9. Topic=(Isolation or Purification)
8. #7 AND #4
7. Topic=(Scavenger*)
6. #5 AND #4
5. Topic=(Agonist* or Antagonist* or Inhibitor*)
4. Topic=(Free Radical* or Peroxide*)
3. Topic=(Oxidation-Reduction) OR Topic=(Oxidant*)
2. Topic=(ascorbic acid or bilirubin or butylated hydroxyanisole or butylated hydroxytoluene or canthaxanthin or carotenoids or catalase or ergothioneine or grape seed extract or melatonin or nordihydroguaiaretic acid or probucol or propyl gallate or pyrogallol

or quercetin or selenium or silymarin or thioctic acid or tocopherols or tocotrienols or uric acid or vitamin e or ealpha-tocopherol or beta-tocopherol or gamma-tocopherol or zeta carotene or beta-carotene or curcumin or methionine or allopurinol)
1. Topic=(antioxidant*)

Appendix 5. Plain language definitions

This appendix contains definitions of specialised terms used in this review to make them more accessible for all users.
Ameliorating: to make or become better.
Anticarcinogenic: a substance that can inhibit or prevent the development of cancer.
Autoimmune pancreatitis: a rare form of pancreatitis thought to be caused by an immunological reaction of the body against its own organs (in this case, the pancreas).
Deleterious: causing harm or damage.
Endocrine pancreatic function: refers to the production of insulin by the pancreas to regulate blood sugar levels.
Epidemiology: science concerning the study of causes and patterns of disease.
Etiology: the cause of a disease.
Exocrine pancreatic function: refers to the production of digestive enzymes of the pancreas.
Lipids: fats.
Macromolecules: very large molecules, usually formed by combinations of many smaller subunits.
Nucleic acids: the building blocks of DNA.
Pancreatic divisum: a congenital anomaly in the anatomy of the ducts of the pancreas in which a single pancreatic duct is not formed, but rather remains as two distinct ducts.
Parenchyme: the body of an organ, used to mainly to distinguish the functional part of an organ from other structures, such as ducts and blood vessels within that organ.
Postprandial pain: pain after meals.
Somnolence: drowsiness.
Steatorhoea: the presence of excess fat in faeces.

CONTRIBUTIONS OF AUTHORS

Ahmed Ali U, Jens S, Busch ORC, Keus F, Gooszen HG and Boermeester MA participated in the design of this review and in drafting of the protocol.

Ahmed Ali U and Jens S performed the search, extracted the data, assessed the studies and drafted the first version of the review.

Ahmed Ali U, Busch ORC, Keus F, van Goor H and Boermeester MA participated in the statistical analysis and in interpretation of the results.

All review authors co-authored the review and read and approved the final manuscript.

DECLARATIONS OF INTEREST

Authors have reported no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- A new secondary outcome (number of pancreatitis events) has been included in the review.

- The protocol described under 'Searching for other resources' that review authors planned to *"request additional information from all authors of included trials on any published, unpublished or ongoing trials, by letter or by e-mail."* This is not included in the review.

- The review authors have included assessment of suitability of cross-over design in the assessment of risk of bias in the review methods.

- The section on data synthesis has been updated with new methods for dealing with parallel/cross-over/combining parallel and cross-over trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [blood; *drug therapy; etiology]; Analgesics [therapeutic use]; Antioxidants [adverse effects; *therapeutic use]; Ascorbic Acid [blood]; Chronic Pain [drug therapy; etiology]; Gastrointestinal Diseases [chemically induced]; Headache [chemically induced]; Pain Measurement; Pancreatitis, Chronic [*complications]; Randomized Controlled Trials as Topic; Vitamin A [blood]; Vitamin E [blood]; beta Carotene [blood]

MeSH check words

Humans